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CONTENTS

Clinical Interpretation of the Middlebrook-Dubos Hemagglutination Test. DAVID T. SMITH AND NANCY B. SCOTT 121

Human Pharmacology of *p*-Formylacetanilide Thiosemicarbazone (Myvizone). GEORGE SIRMONS, LAWRENCE B. HOBSON, ALBERT RESNICK, RALPH DENICOLA, AND RICHARD H. BENNETT 128

The Effect of 4-Acetylaminobenzal Thiosemicarbazone (Tibione) on Experimental Tuberculosis in Guinea Pigs. DAVID M. SPAIN, WILLIAM G. CHILDRESS, AND J. STUART FIEHLER 144

The Effect of Dihydrostreptomycin—Para-aminosalicylate (DHS-PAS) on Experimental Tuberculosis in Guinea Pigs. ALFRED G. KARLSON, JOSEPH H. GAISER, AND WILLIAM H. FELDMAN 149

The Inability of *p*-Aminosalicylic Acid to Delay the Emergence of Streptomycin-resistant Tubercle Bacilli in Mice. ELIZABETH H. WILLISTON AND GUY P. YOUMANS 156

The Clinical Toxicity of Sulphetrone. WILLIAM WEISS AND EMIL BOGEN 160

Vertical Tomography of the Thorax. D. W. CROMBIE AND PAUL M. ANDRUS 170

Experiences with Surgical Reconstruction of the Trachea. PAUL W. GERAUTZ 176

Rehabilitation of the Tuberculous in Philadelphia. A Study of the Effectiveness of the Program of Rehabilitation in Philadelphia for a Ten-Year Period, July 1, 1939 to July 1, 1949. GERTRUDE K. LANGTON, RAYMOND D. WAGNER, AND PAUL MEIER 190

Case Reports:
Miliary Tuberculosis and Pregnancy. GEORGE E. SPENCER, PASCAL D. SPINO, AND J. D. SILVERMAN 209

Eroding Calcified Mediastinal Lymph Nodes. SHEA HALLE AND OSCAR BLITZ 213

Artificial Pneumoperitoneum Complicated by Pregnancy. STANLEY H. SAHN AND HYMAN E. BASS 219

Editorial: The Hemagglutination Test in Tuberculosis. GARDNER MIDDLEBROOK 223

Letters to the Editors: Transmission of Streptomycin-resistant Tubercle Bacilli. HERBERT I. MCCOY 227

Books 228

Abstracts 25

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(1) Thorn, G.W.; Quinby, J.T., and Marshall, C., Jr., Ann. Int. Med. 18:913 (June) 1943.
(2) Orent-Keiles, E., and Halliman, L.F., Circular No. 827, United States Department of Agriculture, Bureau of Human Nutrition and Home Economics, Agricultural Research Administration, Dec., 1949.

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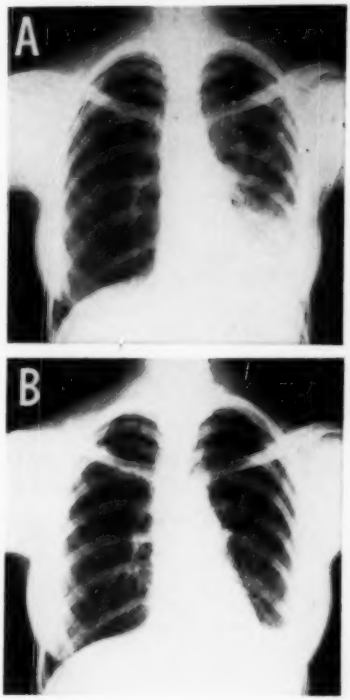

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CLINICAL INTERPRETATION OF THE MIDDLEBROOK-DUBOS HEMAGGLUTINATION TEST[1,2]

DAVID T. SMITH AND NANCY B. SCOTT

(Received for publication April 26, 1950)

In 1948 Middlebrook and Dubos (1) described a hemagglutination test for the detection of antibodies in the serum of patients with tuberculosis and of animals infected with tubercle bacilli. The writers have modified this test by substituting a commerical preparation of tuberculin (2) for the special extract which the original investigators prepared in their own laboratory. During the past fifteen months, 800 tests have been performed on approximately 400 persons by the use of the modified method.

MATERIALS AND METHODS

Approximately 5 ml. of blood are drawn from the patient and allowed to clot at room temperature. The serum is removed after centrifugation and may be used immediately or frozen for future use.

The materials needed for this test are: (*1*) patient's serum; (*2*) Lederle's 4X Tuberculin; (*3*) sheep's blood which has been diluted as soon as it is drawn with equal quantities of modified Alsever's solution[3]; (*4*) Eagle's phosphate buffered saline[4] (This saline usually has a pH of 7.39 to 7.4 but is satisfactory in the range of 7.1 to 7.4. This special saline is used exclusively in the preparation of materials and in the test.); and (*5*) standard serologic 1 and 5 ml. pipettes and standard Wassermann tubes. The amounts of materials described in the following paragraphs are sufficient to perform approximately 10 tests.

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[1] From Departments of Bacteriology and Medicine, Duke University School of Medicine, Durham, North Carolina.

[2] Presented before the Medical Section, as part of the symposium on *Laboratory and Other Basic Research*, at the 46th annual meeting of the National Tuberculosis Association, Washington, D. C., April 26, 1950.

[3] Each 100 ml. of Alsever's solution contains: dextrose, 2.05 gm.; sodium citrate, 0.8 gm.; and sodium chloride, 0.42 gm. The original Alsever formula has been recently modified by the addition of 0.055 gm. of citric acid per 100 ml. The finally sterilized solution has a pH of 6.1 and shows very slight or no evidence of caramelization. (Bukantz, S. C., Rein, C. R., and Kent, J. R: Studies in complement fixation: II. Preservation of sheep's blood in citrate dextrose mixture (modified Alsever's solution) for use in the complement fixation reaction, J. Lab. & Clin. Med., 1946, *31*, 394).

[4] Stock solution of Eagle's buffered saline contains: NaCl, 170 gm.; KH_2PO_4, 2.7 gm.; Na_2HPO_4 (anhydrous), 11.3 gm.; H_2O up to one liter. Dilute 1:20 with distilled water for use. This yields a pH of 7.39 to 7.4 (Eagle H.: Laboratory Diagnosis of Syphilis, C. V. Mosby Company, St. Louis, 1937).

Preparation of Washed, Packed Erythrocytes

Approximately 50 ml. of the mixture of sheep's blood in Alsever's solution are centrifuged for 10 minutes at 1,800 r.p.m. The supernatant is removed with a pipette and discarded. The packed red cells are then diluted with 6 volumes of saline and recentrifuged. After discarding the supernatant, this process is repeated a second time. Although 6 volumes of saline are used for the fourth centrifugation, the rate is increased to 2,000 r.p.m. and the time is extended to 20 minutes. As much as possible of the supernatant is carefully removed with a small pipette, leaving the packed, washed cells. These packed cells should be used in the ensuing 48-hour period.

Sensitization of Red Cells with Tuberculin

Old Tuberculin (Lederle 4X) in 0.4 ml. amounts is added to 5.6 ml. of saline to get a 1:15 dilution of tuberculin. One-tenth ml. of packed, washed red cells is added to the 6 ml. of diluted tuberculin and incubated for 2 hours in a 37°C. water bath. The mixture is shaken thoroughly every 15 minutes during the incubation period. After incubation the mixture is centrifuged at approximately 1,000 r.p.m. for 6 minutes. The low-speed centrifugation is essential to prevent the formation of a hard button of red cells which is difficult to resuspend without hemolyzing some of the cells. After removing the supernatant with a pipette, the cells are resuspended in 6 ml. of saline and centrifuged. This process is repeated a second time. After the third washing all the supernatant is carefully removed and the cells are resuspended in 50 ml. of saline, resulting in an approximately 0.2 per cent suspension. This suspension of cells is used as the antigen in the hemagglutination test. The antigen may be stored up to 3 days at 4°C.

Preparation of Patient's Serum

One ml. of the patient's serum is added to 1 ml. of saline and inactivated at 65°C. for 3 minutes. Since many patients have heterophile antibodies in their serum which may agglutinate normal sheep cells, it is necessary to adsorb these antibodies from the serum. The washed, packed, normal unsensitized red cells are added in 0.3 ml. amounts to each tube containing the serum saline mixture and the tube is shaken immediately. It should be noted that red cells permitted to dry on the sides of the tube will hemolyze and thus impart a red color to the serum. Partial hemolysis in serum does not in itself effect the hemagglutination titer, but makes reading of the tests more difficult. The patient's serum with red cells added is allowed to stand at room temperature for at least 20 minutes. The cells are removed from the serum by centrifugation at 2,500 r.p.m. for 7 minutes and discarded. Another 0.3 ml. volume of untreated, packed red cells is added to the serum and the mixture is shaken and allowed to stand for another period of 20 minutes at room temperature, after which the cells are removed by centrifugation. Occasionally two consecutive adsorption procedures do not remove all of the heterophile antibodies from the serum; and in these instances, when clumping of the red cells is observed following the second adsorption, a third 0.3 volume of red cells is added, permitted to stand, and separated from the serum before the serum is used in the hemagglutination test.

Adsorbed serum may be stored indefinitely in a deep freeze, without alteration of antibody titer to sensitized red cells.

Hemagglutination Test

Using standard size Wassermann tubes and racks, tests are set up with adsorbed serum in twofold serial dilutions. Four-tenths ml. of the adsorbed serum is added to the first and second tubes. Serial dilutions are made from the second tube through eight tubes, with equal volumes of saline. To tubes containing 0.4 ml. of serum dilution there is added 0.4 ml. of 0.2 per cent suspension of sensitized red cells.

Four controls are necessary for the proper evaluation of the test: (*1*) As a control for spontaneous clumping of the antigen, 0.4 ml. of sensitized red cell suspension, used as the antigen, is added to 0.4 ml. of saline. (*2*) As a control for incomplete adsorption of heterophile antibodies, 0.4 ml. of the 1:2 dilution of adsorbed serum is added to 0.4 ml. of a 0.2 per cent suspension of normal, unsensitized, washed sheep cells. (*3*) and (*4*) are controls for the proper sensitization of the red cells by the tuberculin. Titered tests are performed with a known positive and a known negative serum with each group of unknown sera.

The tubes are shaken and then incubated in a 37°C. water bath for 3 hours. Upon removal from the water bath, tubes are reshaken and left at room temperature overnight to be read the following morning. At this time the red cells are found in a button at the bottom of the tube. All tests are read directly with the eye without aid of magnification. In reading the tests each tube is shaken gently to resuspend the cells. It has been found that the agglutinated red cells in the "positive" tubes may be dislodged from the bottom of the tube readily and appear as clumps in the fluid. The shaking should be discontinued as soon as all cells have left the bottom of the tube because continued shaking breaks the clumps into smaller and smaller units. The cells in the "negative" tubes are more difficult to resuspend and require more shaking to clear all the cells from the bottom of the tube and produce a homogenous suspension.

RESULTS

Results in patients with active tuberculosis: The sera of 104 patients, in whom the diagnosis of tuberculosis was established by the demonstration of tubercle bacilli, were examined and in 83, or 80 per cent, hemagglutinins were demonstrated. Nearly all of the patients with negative reactions had far advanced disease with a poor prognosis. The test was positive, also, in an additional group of 6 patients with typical symptoms and signs of tuberculosis but in whom tubercle bacilli could not be demonstrated. With one or two exceptions, tuberculin tests were not performed on these 110 patients. The titers obtained in the sera of 23 of 24 consecutively tested sanatorium patients are shown in table 1.

Results in healthy and sick persons with negative tuberculin tests: The sera from 28 healthy persons with negative tuberculin tests were examined and 26 were found negative to the hemagglutination test. The sera from 11 patients, ill with various diseases but having negative tuberculin tests, were negative also to the hemagglutination test.

Results in patients with long-arrested tuberculosis: The sera from 10 persons, known to have had active tuberculosis which had been arrested for a long period,

were examined, and 8 of the 10 were negative. One person with a negative test was still negative twelve months later but became positive seven days after the performance of a tuberculin test.

Results in patients with positive serologic tests for syphilis: Sera from 22 consecutively studied patients with positive serologic tests for syphilis were examined and 18 of the 22 were found to be negative for hemagglutinins. The remaining 4 patients with positive hemagglutination tests were not studied in sufficient detail to eliminate the possibility of active tuberculosis.

Results in healthy individuals with positive tuberculin tests: An unexpected finding was the observation that 36 of 71 healthy persons (50 per cent) with positive tuberculin tests also had positive hemagglutination tests. This was in striking contrast to the results in the 26 of 28 normal persons with negative skin tests who had no antibodies in their blood.

TABLE 1

Results of Hemagglutinations Showing Titers Obtained on Sera from One Group of Sanatorium Patients

SERUM DILUTIONS GIVING POSITIVE HEMAGGLUTINATIONS	PATIENTS																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1:2	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
1:4		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+		+	+
1:8		+	+	+	+	+	+	+	+	+		+	+	+	+			+	+	+			+	
1:16		+	+		+	+	+	+	+	+			+	+				+		+			+	
1:32		+	+				+	+	+	+			+	+						+			+	
1:64		+					+	+		+			+	+										
1:128		+						+																
1:256																								

Similar results were obtained in patients ill with diseases other than tuberculosis but who had positive tuberculin reactions. It was found that 6 of 10 such patients had positive hemagglutination tests. The large percentage of positive antibody tests in this group of normal persons and patients, who had no clinical evidence of tuberculosis, suggested the possibility that antibodies had been stimulated by the injection of tuberculin since in most instances the tuberculin test was performed prior to the collection of serum for the test.

A study of normal individuals before and after the administration of tuberculin tests: A group of 84 medical and technical students volunteered to cooperate in a study designed to evaluate the effect of the tuberculin test on the antibodies which are measured by the hemagglutination test. Sera were collected from all 84 before the tuberculin skin tests were performed. Among this group 13, or 15 per cent, had a positive hemagglutination test. Twelve of the 13 were later found to have a positive skin test to tuberculin. All 13 were still positive after the tuberculin test; the titers remaining the same in 6, decreasing in 3, and increasing in 4.

For one reason or another 3 students failed to complete all of the studies, leaving 68 who were known to have negative hemagglutination tests before the tuber-

culin tests were performed. Sera were collected one week after one or more tuberculin tests with 1:1,000 (0.1 mg.), 1:100 (1 mg.), or 1:10 (10 mg.) OT. Of this group 19, or 28 per cent, were found to have a positive hemagglutination test. Of the 19 who developed hemagglutinins, 15 had a positive and 4 had a negative tuberculin test. Of the 49 who failed to show hemagglutinins after "stimulation" with tuberculin, 31 had positive and 18 had negative tuberculin tests.

When these data are rearranged it is found that positive tuberculin reactions were elicited in 58 students, and sera collected after the tuberculin reactions showed that 27, or 49 per cent, had positive hemagglutination titers. This corresponds closely to the 52 per cent found in the 81 tuberculin-positive healthy individuals and patients with diseases other than tuberculosis, when the sera were collected after the stimulation of a tuberculin reaction.

Effect of BCG inoculation on hemagglutinin titers: Thirteen of the 18 students with negative hemagglutination tests and negative tuberculin reactions to 1:100 (1 mg.) OT were given BCG and bled seven weeks later before the application of the repeat tuberculin test. Ten of the 13 were found to have positive hemagglutination titers and 3 were negative, although all 13 now had positive tuberculin reactions to 1:100 (1 mg.) OT. One of the 3 students with a negative reaction was found to have a positive hemagglutination test three months later.

In a previous group of 39 medical and nursing students who received BCG vaccination, 30 were found to have positive hemagglutinins four to five months after immunization. In 4 instances, students failed to develop positive tuberculin tests after vaccination but did show hemagglutinins. Eight students had positive skin tests and negative hemagglutinins.

One student who developed both a positive skin test and hemagglutination was retested one year later and at that time it was found that the tuberculin reaction was negative but the hemagglutinins remained positive.

Hemagglutinins in patients with sarcoidosis: A total of 11 patients with sarcoidosis were tested for hemagglutinins. In each case the diagnosis was based on typical clinical and histologic findings and all of the patients failed to react to the intradermal injection of 1:100 dilution of OT. Seven of the 11 had positive hemagglutinins in the same range as patients with tuberculosis, and 4 were negative. In all but 2 cases tuberculin tests had been given shortly before blood was drawn for the hemagglutination tests. In these 2 instances, the patient with symptoms had a positive hemagglutination test and the one without symptoms was negative. One patient, who had a high titer while ill, showed no hemagglutinins one year later after the acute symptoms had disappeared. Since it has been found that a tuberculin test may induce the appearance of hemagglutinins, a series of cases of sarcoidosis should be studied in which the blood is collected before the skin test is applied.

DISCUSSION

Many patients with clinically active tuberculosis have antibodies in their blood which give a positive hemagglutination test. The test is usually negative in the far advanced type of case with poor prognosis and also in the patient with

disease which has been arrested for a long period. In the first instance, it may be assumed that the antibodies have been neutralized by the adsorption of products produced by the rapidly growing tubercle bacilli, and in the second instance the agglutinins are absent because there is no longer sufficient antigenic stimulation from the healed tuberculous lesions.

Normal persons who have recently converted from a negative to a positive tuberculin, and individuals who have been vaccinated with BCG, frequently have a positive hemagglutination test. But some persons develop a positive tuberculin test following BCG inoculation without developing detectable antibodies, while a smaller number have a positive hemagglutination test and a negative tuberculin test.

Apparently the hemagglutinins gradually disappear following a subclinical primary infection, although no data are available from the present study with which to calculate the rate of disappearance. The gradual disappearance of the hemagglutinins is suggested by the observation on the healthy medical and technical students who had positive tuberculin tests. It may be assumed that all students with positive tuberculin tests have had a primary tuberculous infection. Among 58 students with positive tuberculin reactions, 12, or 22 per cent, had positive hemagglutination tests before "stimulation" with tuberculin. Of the remaining 46, a total of 15, or 32 per cent, had had no hemagglutinins before "stimulation" by tuberculin and had positive titers after "stimulation." The final 31, or 67 per cent, were not "stimulated" by tuberculin to produce hemagglutinins.

Of equal interest are the 5 students in this study who had positive hemagglutinin titers but negative tuberculin tests, and the 4 in a previous group of 39 vaccinated with BCG who developed positive hemagglutinins but failed to react to the intracutaneous injection of 1:100 (1 mg.) OT. The question may be raised whether these are examples of infection followed by the development of immunity but without the acquisition of allergy.

It is possible that the hemagglutination test measures immunologic activity or, more specifically, precipitins in the blood which react with a carbohydrate fraction of the tubercle bacillus (1). The test is usually negative when the patient's infection has been arrested for a long period, presumably because there is insufficient antigen available in the body to stimulate antibody production. The hemagglutination test is also negative in most far advanced cases with poor prognoses, possibly because an excess of antigen is produced by the rapidly growing tubercle bacilli which neutralizes the circulating antibodies.

No final conclusions can be drawn until more is known about the nature of the test and its limitations. The possibility of biologically false positive or false negative reactions has not yet been eliminated.

SUMMARY

The Middlebrook-Dubos hemagglutination test as performed in this laboratory is not a test for determining the "clinical activity" of a tuberculous lesion. Positive tests were found in 13 of 84 healthy students when the sera were collected

before a tuberculin test was performed. Among 68 students with a negative hemagglutination test before "stimulation" with tuberculin, 19 were found to have positive titers after "stimulation."

On the other hand, patients with clinically active tuberculosis and good prognoses usually have positive hemagglutination titers. Furthermore, students who have negative tuberculin reactions and negative hemagglutinin tests, even after repeated testing with tuberculin, usually develop hemagglutinins after vaccination with BCG.

SUMARIO

Interpretación Clínica de la Prueba de Hemaglutinación de Middlebrook-Dubos

La prueba de hemaglutinación de Middlebrook-Dubos, tal como se ejecuta en el laboratorio de los AA., no se aplica a la actividad clínica. La prueba resultó positiva en 13 de 84 estudiantes sanos, en que se recogió el suero antes de verificar una reacción a la tuberculina. Entre 68 estudiantes con pruebas negativas de hemaglutinación antes de la excitación con tuberculina, 19 mostraron títulos positivos después de tal excitación.

Por otro lado, enfermos con tuberculosis clínicamente activa y buen pronóstico suelen revelar títulos positivos de hemaglutinación. Además, los estudiantes negativos para tuberculinas y hemaglutininas, aun después de comprobación repetida con tuberculinas, suelen revelar hemaglutininas después de la vacunación con BCG.

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HUMAN PHARMACOLOGY OF *p*-FORMYLACETANILIDE THIOSEMICARBAZONE (MYVIZONE)[1]

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INTRODUCTION

The antituberculous effectiveness of *p*-formylacetanilide thiosemicarbazone (TB 1/698) has been reported by European investigators (1, 2, 3, 4) and confirmed, in experimental tuberculosis, by Donovick and Bernstein (5). The pharmacology of the compound was studied in animals by Domagk (6) and by Burke and Titus (7). The latter also described physicochemical methods for determining the concentration of the agent in blood, urine, and tissues.

Although several reports in the German literature (3, 4) deal with the toxic effects of TB 1/698, it was considered to be advisable to undertake a study of the pharmacology of the compound in humans prior to more extensive clinical trials in this country. In the pharmacologic study, it was decided to employ a maximal daily dose of 800 mg. The German investigators had reported no fatalities ascribable to the drug when this dosage was administered to adults; yet toxic reactions could be anticipated. The maximal daily dose selected for the patients represented 10 to 25 mg. per kg. of body weight and was far less than the 65 mg. per kg. per day tolerated for several weeks by mice (5) or the 200 mg. per kg. per day which Burke and Titus (7) administered safely to dogs. The doses were larger, however, than those currently employed in the routine treatment of patients (3, 4).

MATERIALS AND METHODS

The 8 men and 8 women selected for treatment all had long-standing, extensive, bilateral, cavitary, pulmonary tuberculosis and most of them had been treated previously with streptomycin. There was a persistent trend toward progression of the lesions in most cases during the months prior to therapy, and the sputum of each patient consistently contained large numbers of tubercle bacilli. None of the patients was a candidate for any other form of active treatment; all remained on the usual sanatorium regimen throughout the trial. Some time prior to administration of the drug two patients (*A Wa, R Ro*) had had therapeutic pneumoperitoneum induced and this was continued. The clinical data and dosage regimens are reviewed in table 1.

The *p*-formylacetanilide thiosemicarbazone (Myvizone) was administered orally in capsules containing 25 mg. or 100 mg. of the drug. No more than 200 mg. were given at any one time during the day. The 16 patients were divided into four groups, each consisting of 2 men and 2 women. The first group was given 25 mg. of Myvizone daily at the start; the second received daily 50 mg. initially; the third, 100 mg.; and the fourth, 200 mg. The dosage was doubled every three days until every patient who tolerated the larger doses was receiving 800 mg. daily in four divided doses. Thus, after six to fifteen days, all of the men and 5 of the 8 women were given the maximal dosage.

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Several patients showed significant evidence of toxicity on the maximal dose and it was decided to reduce the daily medication of all patients to 400 mg. This was done after the women had received 800 mg. for a maximum of thirteen days and the men, for a maximum of twenty-nine days. The course of Myvizone therapy for each patient is indicated in table 1.

The treatment of many patients was somewhat intermittent because of toxic reactions; 4 women (*J Cl, L Wa, J Go, V Pf*) could not continue therapy even on smaller doses. The treatment period extended from seven to ninety-three days for the female patients, with a total Myvizone intake of 1.3 to 40.8 gm.; only 4

TABLE 1

Clinical Data and Myvizone Dosage Regimens

PATIENT	SEX	AGE	RACE	WT.	INITIAL DAILY DOSE	MAXIMAL DAILY DOSE	MAXIMAL DAILY DOSE	TOTAL DOSE	TREATMENT PERIOD	DAYS OF TREATMENT	DAYS ON 800 MG.	ROENTGENOGRAPHIC STATUS	
												Prior to treatment	At completion of treatment
		yrs.		*kg.*	*mg.*	*mg.*	*mg./kg.*	*gm.*	*days*				
J Mc	M	27	W	50	200	800	16	52.8	108	107	29	P	I
M Ca	M	42	N	67	200	800	12	49.4	108	100	30	S	I
R Ro	F	32	W	47	200	800	17	40.4	93	93	12	P	S
M Si	F	38	N	60	200	800	13	40.8	93	93	13	S	I
J Jo	M	50	W	67	100	800	12	35.6	108	71	27	S	S
B Cl	M	49	W	70	100	800	11	32.2	70	65	27	S	X
J Cl	F	36	W	32	100	800	25	9.8	30	28	4	P	S
L Wa	F	48	W	41	100	400	10	1.3	7	7	0	P	X
T Ob	M	42	W	76	50	800	10	48.6	108	108	24	S	I
A Le	M	55	W	50	50	800	16	34.3	108	87	13	S	S
E Ha	F	33	W	50	50	800	16	17.6	93	73	2	S	S
J Go	F	32	W	60	50	800	13	7.7	71	32	3	P	S
T Ma	M	38	W	72	25	800	11	45.1	108	108	15	S	S
J Ro	M	27	W	55	25	800	15	25.8	108	75	12	P	X
A Wa	F	28	N	33	25	400	12	27.9	92	86	0	P	I
V Pf	F	33	W	37	25	400	11	3.0	64	25	0	P	S

M, male; F, female; W, white; N, Negro; P, progressive; S, stationary; I, improved; X, worse.

women (*R Ro, M Si, E Ha, A Wa*) were treated for more than thirty consecutive days. The men received the drug over a period of seventy to one hundred and eight days with total dosages of 25.8 to 52.8 gm.

In addition to the usual clinical observations and monthly chest roentgenograms, the following laboratory examinations were made prior to treatment and during the course of Myvizone: (*1*) Complete blood counts with hematocrit and erythrocyte sedimentation determinations were performed each week. (*2*) Renal function was evaluated by urinalyses once or twice each week, with blood urea nitrogen determinations twice a week and phenolsulfonephthalein excretion tests every other week. Since neither the blood urea nitrogen nor the phenolsulfonephthalein test showed any significant change during the first two

months of treatment, these two tests were discontinued at that time. (3) Hepatic function was evaluated by weekly determinations of the cephalin flocculation reaction, the plasma protein content, and the albumin-globulin ratio. These were supplemented, when indicated, by determinations of the thymol turbidity reaction, prothrombin time, icterus index, and urobilinogen excretion. The excretory function of the liver was not tested routinely.

Sputum smears and cultures were examined every two weeks. The sensitivity of the bacilli to Myvizone, streptomycin, and *p*-aminosalicylic acid was determined in each culture. The tests were carried out by subculturing in liquid media containing the agent. The details of the methods used for Myvizone will be reported elsewhere (8).

OBSERVATIONS

Clinical Evidence of Toxicity

In table 2 are tabulated the principal toxic reactions with the day of treatment, the total dosage received, and the current daily dose at the time of the initial appearance of each reaction.

Malaise: The most frequent symptom attributable to Myvizone was a vague sensation generally characterized as "a grippy feeling," sleepiness, lassitude, or inability to concentrate. The sensation usually appeared early, then disappeared after two to five days even though medication was continued. It was experienced by 13 patients between the seventh and twenty-ninth days. At the time the symptom appeared one woman was receiving 100 mg. daily and had had a total of only 320 mg.

Malaise generally appeared earlier, on smaller daily dosage and after a lower total dosage, in women than in men. In 9 of the patients (*R Ro, J Jo, B Cl, J Cl, A Le, E Ha, J Go, J Ro, V Pf*), malaise preceded by one to twelve days the detection of a toxic reaction which necessitated the discontinuance of treatment or a reduction of dosage. Later in the study, this symptom was considered the initial sign of toxicity and the dosage was reduced when it appeared in patients *M Ca, M Si, T Ob,* and *T Ma.*

Nausea and vomiting: Nausea was experienced by 10, and vomiting by 6, patients while taking Myvizone. These symptoms varied in severity and in 2 instances (*J Cl, L Wa*) probably were not due solely to the medication. Nausea and vomiting were experienced more frequently by those patients who were given the smaller initial doses of the drug. Two women (*J Go, V Pf*) had severe vomiting during the second week of treatment and became dehydrated. They were receiving respectively 400 and 800 mg. of Myvizone daily at the time but had started on 50 and 25 mg. initially. Another woman (*A Wa*) had persistent, severe nausea without vomiting. These symptoms disappeared when the dosage was reduced or treatment was discontinued. Every patient who had severe nausea definitely related to the ingestion of the drug had an abnormal cephalin flocculation test which returned to normal subsequently.

Anorexia and constipation: Five patients (*R Ro, J Jo, A Le, J Ro, V Pf*) experienced transient anorexia between the fourth and twenty-third days of Myvizone therapy. Two others (*T Ma, J Go*) noted no change in appetite, and 7 patients (*J Me, M Ca, M Si, J Cl, T Ob, E Ha, A Wa*) reported that their appetites improved during treatment.

TABLE 2

Toxic Reactions to Myvizone

PATIENT	SEX	MALAISE OR LISTLESSNESS	NAUSEA	VOMITING	LOSS OF TASTE	DERMATITIS	HEPATIC DYSFUNCTION*	ANEMIA**
J Me	M							
M Ca	M	**29**(20.2) 800		**27**(18.6) 800				
R Ro	F	**12**(6.6) 800					**17**(10.6)† 400	**40**(19.2) 400
M Si	F	**7**(2.6) 800						**40**(19.6) 400
J Jo	M	**14**(6.1) 800			**15**(6.9)‡ 800			**34**(22.1) 800
B Cl	M	**15**(6.9) 800	**47**(27.1) 400	**47**(27.1) 400	**25**(14.9) 800	**19**(10.1) 800	**57**(29.3)‡ 400	**27**(16.5)§ 800
J Cl	F	**10**(2.2) 800	**13**(4.6)§§ 400				**17**(5.4)‡ 400	**19**(6.6) 400
L Wa	F		**4**(0.5)§§ 200	**6**(0.9) 200			**0**‡	
T Ob	M	**21**(9.4) 800						
A Le	M	**21**(9.4) 800	**21**(9.4) 800	**6**(0.45) 100		**26**(11.8)‡ 800		
E Ha	F	**5**(0.35) 100	**15**(4.6)‡ 800			**26**(5.8) 400	**17**(5.4)‡ 400	
J Go	F	**5**(0.35) 100	**12**(2.2)‡ 800	**12**(2.2)‡ 400		**15**(4.6)‡ 800	**17**(4.6) 800	
T Ma	M	**29**(13.5) 800	**15**(2.3)‖ 800					
J Ro	M	**21**(7.1) 800	**19**(5.5) 800				**29**(11.1) 800	**27**(11.1)‡ 800
A Wa	F		**12**(1.1)† 200				**17**(2.7) 200	
V Pf	F	**7**(0.32) 100	**9**(5.2) 100	**13**(1.5)‡ 400			**17**(2.3) 400	
Total number of patients showing reactions		13	10	6	2	4	8	6

Bold-faced figures indicate day in therapeutic regimen on which reaction first appeared.

Figures in parenthesis indicate total Myvizone intake in grams at time reaction first appeared. Figures below these are daily dosage in milligrams at time reaction first appeared.

* Positive cephalin flocculation test or A/G ratio less than 1.0.

** RBC less than 4 million.

† Dosage reduced because of findings.

‡ Treatment discontinued because of findings (later resumed except patients B Cl and L Wa).

§ With hemoptysis but persistent thereafter.

§§ Present before treatment.

‖ Occurred only when drug was taken on empty stomach.

Constipation occurred at some time during the Myvizone therapy of 8 patients (*J Me, M Ca, R Ro, J Jo, J Cl, T Ob, J Ro, A Wa*) but never was so persistent or severe as to require change of the dosage. Six other patients never experienced constipation and none had diarrhea attributable to the medication.

Anorexia and constipation could not be evaluated in the case of patient *B Cl*, who had prolonged hemoptysis, nor of *L Wa* who received a very short course of therapy.

Abdominal discomfort: Three men experienced discomfort in the epigastric region which they described as "heart burn." Two (*M Ca, B Cl*) had concomitant vomiting; the third (*J Ro*) had diarrhea and vomited a few days later. It was believed that the latter may have had a mild, acute gastroenteritis not due solely to the medication. The discomfort occurred respectively on the twenty-seventh, fifty-first, and sixty-sixth days after the start of therapy and persisted for only a short time.

Loss of taste: Two patients (*J Jo, B Cl*) gradually lost the sense of taste, beginning respectively on the fifteenth and twenty-fifth days of Myvizone therapy. In both, this disturbance involved the entire surface of the tongue including the base. One man (*B Cl*) was totally unable to distinguish sweet, salty, or bitter solutions. The other (*J Jo*) was unable to identify sweet solutions; he perceived salty and sour solutions imperfectly and bitter solutions normally. There probably was some concomitant loss of the sense of smell, and the flow of saliva was diminished; no other neurologic abnormalities could be demonstrated. The impairment gradually improved on withdrawal of the drug, sensation being restored first at the base of the tongue. Restoration was complete within two to four weeks.

Dermatitis: Four patients had well-defined toxic exanthems. In one patient (*A Le*) a generalized, pruritic, erythematous, confluent, macular eruption appeared over the extremities and trunk on the twenty-sixth day of therapy. The face, palms, and soles were diffusely erythematous and maculae were present on the oral mucosa. Similar, but less extensive, lesions were encountered on the extremities in the 3 other patients (*B Cl, E Ha, J Go*) and in 2 other patients (*R Ro, A Wa*) pruritis was experienced without visible lesions. In 2 patients (*A Le, B Cl*) the dermatitis was preceded by intense palmar itching. All of these manifestations occurred when the daily dose of Myvizone was 400 mg. or more. In 2 instances it was believed necessary to discontinue the medication; in all instances the skin changes subsided when treatment was stopped; and in none was there a recurrence when treatment was resumed. The 2 patients (*B Cl, A Le*) with the most severe exanthems subsequently shed their finger nails which were replaced by new nails during the process.

Two patients (*J Ro, A Wa*) complained of conjunctival itching early in the course of Myvizone. Tearing was the only objective evidence of conjunctivitis.

Hepatic dysfunction: Abnormal results were obtained from tests of hepatic function in 8 patients during the course of therapy. These abnormalities were detected on the seventeenth day of treatment in the 6 females and on the twenty-ninth and fifty-seventh days in the 2 male patients affected. The serum of all these patients gave cephalin flocculation reactions of 1 to 4 plus and the thymol turbidity reaction was similarly altered. The albumin-globulin ratio was less than

unity in 3 patients (*B Cl, J Cl, A Wa*) but the icterus index and prothrombin time were normal in 7. The eighth patient (*J Ro*) had an abnormal cephalin flocculation test during an episode of hemolytic anemia with an elevated icterus index. Evidence of hepatic dysfunction was detected in the 6 women and in one of the men (*J Ro*) while they were taking 800 mg. of Myvizone daily. The other man (*B Cl*) was receiving 400 mg. In every instance the abnormal findings disappeared when the medication was interrupted, the cephalin flocculation reaction becoming normal within a week after discontinuation of the medication. When the dosage was only reduced, the return to normal was slower. Resumption or continuance of treatment with lower doses did not lead to reappearance of the abnormal findings.

One patient (*L Wa*) had an albumin-globulin ratio less than unity as the only evidence of hepatic dysfunction prior to the start of therapy, and subsequently was found to have extensive amyloidosis involving the liver and kidneys. She received Myvizone in doses of 100 mg. daily for three days, 200 mg. for three days, and 400 mg. for one day. Although medication was then stopped, the preexisting hepatic damage gradually became more evident. She expired seventy-eight days after therapy was discontinued.

Anemia: The erythrocyte count fell below 3,500,000 in only 3 patients (*J Cl, B Cl, J Ro*). The erythrocyte count and the hemoglobin concentration of these 3 individuals throughout the course of therapy is plotted in figure 1.

One man (*J Ro*) developed frank hemolytic anemia with icterus while receiving 800 mg. of Myvizone daily. The anemia responded promptly to cessation of the drug followed by transfusions, iron, and vitamin B_{12} medication (see figure 1). His tuberculosis was so severe that Myvizone was started again, in smaller doses, thirty days after the appearance of hemolysis. Although he remained somewhat anemic, there was no further detectable hemolysis. The 2 other patients developed microcytic anemia while receiving 800 mg. and 400 mg. of Myvizone, respectively. One (*B Cl*) became anemic during an episode of prolonged hemoptysis unrelated to his therapy, but the anemia persisted despite antianemic measures during continued Myvizone treatment for two months after hemoptysis had ceased. The other patient (*J Cl*) responded to transfusions and vitamin B_{12} after Myvizone was discontinued.

All of the patients treated for as long as three weeks had a decrease in the number of erythrocytes, the hemoglobin concentration, and the hematocrit. This decrease generally was detectable during the third week of therapy at a time when the daily dosage was 400 or 800 mg. of Myvizone. The findings then remained unchanged or improved in most patients even though medication was continued. There was further hematologic improvement after the drug was stopped for other reasons.

Granulocytopenia was not encountered in any of the 16 patients. In one patient (*J Jo*) the total leukocyte count fell to 3,350 per cu.mm. on one occasion only, but 65 per cent of the white cells were polymorphonuclear leukocytes. In no other instance did the leukocyte count fall below 5,000 per cu.mm.

Albuminuria: The only evidence of renal abnormality attributable to Myvizone therapy was albuminuria in 4 women (*M Si, E Ha, J Go, A Wa*). It disap-

peared either on continued therapy or after medication was stopped for other reasons.

Relation of dosage to toxicity: Review of the dosage data in table 1 and of the reactions noted in table 2 shows that the evidence of severe toxicity first appeared while the patients were receiving 400 or 800 mg. of Myvizone daily. Malaise and mild nausea or vomiting were experienced by some patients while receiving smaller doses of the drug. When patients receiving the same quantity

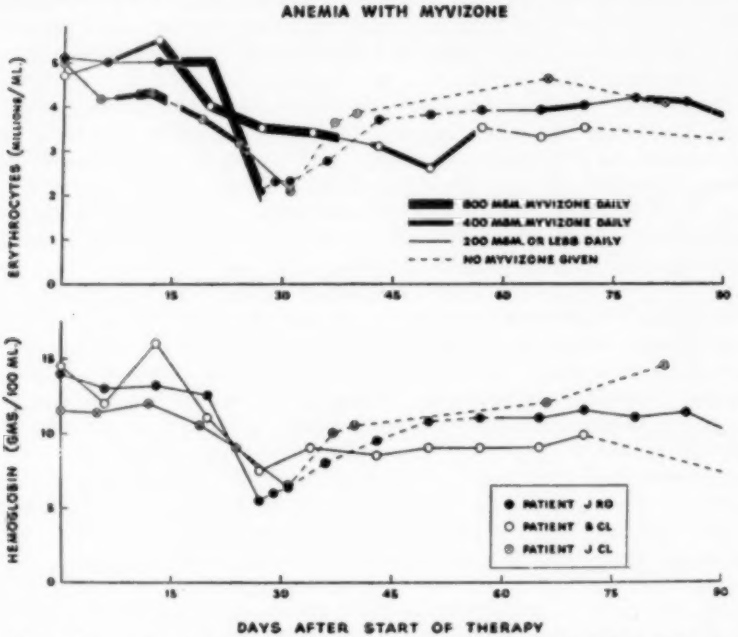

FIG. 1. Severe anemia during Myvizone therapy. Patient *J Ro* had hemolytic anemia for which he received transfusions, iron, and vitamin B_{12} after the twenty-seventh day. Patients *B Cl* and *J Cl* had microcytic anemia which in patient *B Cl* appeared during prolonged hemoptysis. Daily dosage is indicated by width of lines in upper set of curves; details of dosage are not indicated in the lower set of curves.

of Myvizone are compared, no correlation can be demonstrated between the daily dosage in milligrams per kilogram of body weight and the time of appearance or the severity of toxic reactions.

Absorption and Excretion of Myvizone

Five adult tuberculous patients who were not at the time being treated with Myvizone were given 200 mg. of the drug orally in a single dose. Blood samples were drawn at intervals thereafter and assayed for *p*-formylacetanilide thio-

semicarbazone by ultraviolet spectrophotometry (7). The results, plotted in figure 2, indicate that demonstrable concentrations may persist for as long as twenty-four hours. The drug, therefore, is either absorbed slowly from the intestinal tract or removed slowly from the blood stream.

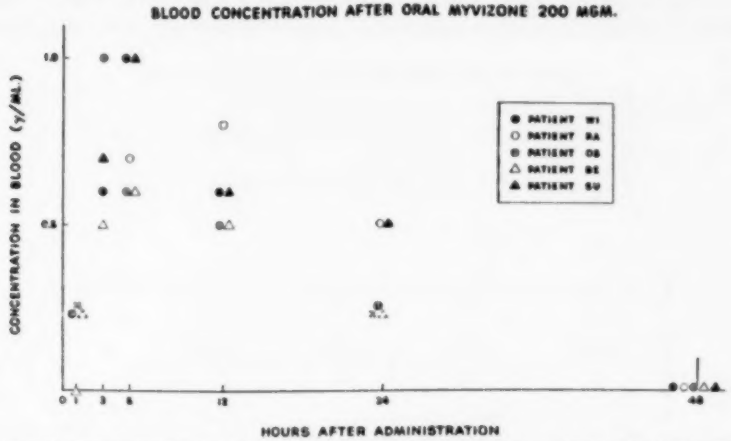

FIG. 2. Concentrations of *p*-formylacetanilide thiosemicarbazone in the blood of patients given 200 mg. of Myvizone by mouth in a single dose at 0 hour. They were not currently under treatment with the drug. Incompletely outlined or shaded symbols indicate concentrations greater than 0 but less than 0.5 γ per ml., the exact amount not having been determined. Determinations were made by ultraviolet spectrophotometry.

TABLE 3

Recovery from Urine of p-Formylacetanilide Thiosemicarbazone after Oral Administration of 200 mg.

PATIENT	PER CENT OF 200 MG. DOSE RECOVERED		
	0 to 24 hours	24 to 48 hours	Total
Wi	16.7	11.5	28.2
Ra	23.8	18.5	42.3
Os	26.2	14.3	40.5
Be	8.5	5.7	14.2
Su	24.0	14.2	38.2

The urine of these patients was collected for the two succeeding twenty-four-hour periods after the single dose. The proportion of the oral dose recovered from the urine is tabulated in table 3. The results indicate significant retention of the drug within the body for longer than twenty-four hours.[2] They also suggest that

[2] A tuberculous lung lobe, removed three hours after the patient was given a single oral dose of Myvizone, 200 mg., contained approximately 1.5 γ of *p*-formylacetanilide thiosemicarbazone per gm. of wet tissue.

there is some route, such as conversion to another compound, by which the drug is removed from the blood in addition to its excretion by the kidneys.

Six of the patients who had received 800 mg. of Myvizone daily for at least two weeks were given, as usual, 200 mg. each at 8 a.m., noon, and at 4 and 8 p.m. Blood samples were drawn at 8 and 11 a.m. and at 8 and 11 p.m. The concentration of *p*-formylacetanilide thiosemicarbazone was determined by ultraviolet

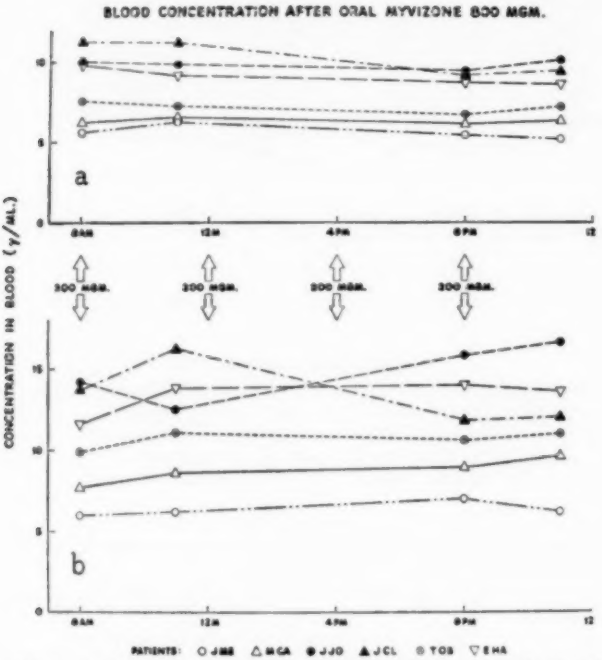

FIG. 3a. Concentrations of *p*-formylacetanilide thiosemicarbazone in the blood of patients routinely receiving 800 mg. of Myvizone daily by mouth in four doses as shown. Determinations were made by ultraviolet spectrophotometry.

FIG. 3b. Concentrations of aromatic amines, calculated as *p*-formylacetanilide thiosemicarbazone, in the same blood samples as those reported in figure 3a. Determinations were made by a modification of Bratton-Marshall technique.

spectrography as before. After hydrolysis of the samples, the content of aromatic amines was determined by a modification of the Bratton-Marshall colorometric method (7). The results are plotted in figure 3.

The Bratton-Marshall method (figure 3b) frequently gave values, expressed in micrograms of *p*-formylacetanilide thiosemicarbazone, significantly greater than those obtained spectrophotometrically (figure 3a). This probably indicates that Myvizone is partially converted in the body to an aromatic amine derivative in

which the thiosemicarbazone portion of the molecule has been modified or destroyed.

There is further support for this hypothesis in the relatively low renal excretion of *p*-formylacetanilide thiosemicarbazone. The content of the drug in the urine passed during the twenty-four-hour period after the first dose on the test day is reported in table 4.

TABLE 4

Recovery from Urine of p-Formylacetanilide Thiosemicarbazone during 24 Hours after First 200 Mg. Dose of 800 Mg. Administered in Four Doses at Four-hour Intervals

PATIENT	MG. RECOVERED	PER CENT OF 800 MG. DOSE RECOVERED
J Me	110	13.8
N Ca	190	23.8
J Jo	401	50.3
B Ce	336	42.0
T Ob	252	31.5
T Ma	226	28.1

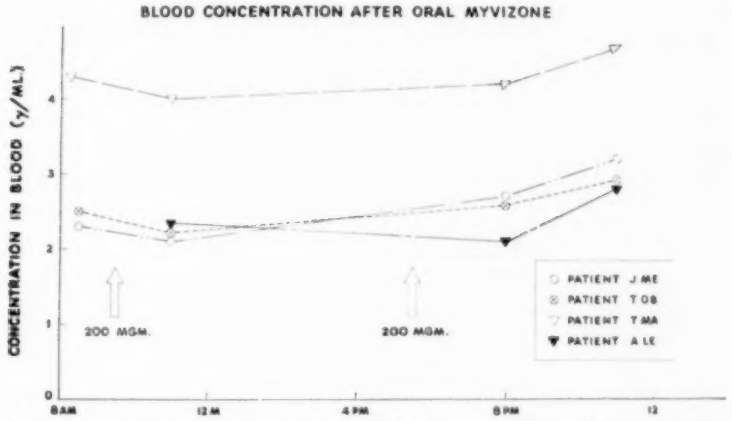

FIG. 4. Concentrations of *p*-formylacetanilide thiosemicarbazone in the blood of patients receiving routinely 400 mg. of Myvizone daily by mouth in two doses as shown. Determinations were made by ultraviolet spectrophotometry.

Later in the study the daily dose of Myvizone was reduced to 400 mg. Determinations were made on 4 patients after they had been on this reduced dosage for a week. Each was given, as usual, a dose of 200 mg. of the drug at about 9:30 a.m. and again at 5:30 p.m. Blood samples were drawn before the first dose and at 11 a.m., 8 p.m., and 11 p.m. The concentration of *p*-formylacetanilide thiosemicarbazone was determined by ultraviolet spectrophotometry and the results are charted in figure 4. The drug content of the urine passed during the twenty-four-hour period after the first dose is reported in table 5.

Heilmeyer and Heilmeyer (9) have reported the maximal serum concentration of *p*-formylacetanilide thiosemicarbazone to be 2 γ per ml. four hours after an oral dose of the drug, presumably 300 mg. Traces of the compound were detected in the serum twenty-four hours after medication. Their method determines the concentration of aromatic amines, and the dose employed was larger than that administered in this study (figure 2).

There is no correlation between the blood concentration of the drug (figures 3 and 4) and the dosage in milligrams per kilogram (table 1). A correlation may be present, however, between the blood concentration of the drug and the severity of the toxic reactions. Thus, patients *J Mc*, *M Ca*, and *T Ob* all had relatively low blood concentrations and tolerated Myvizone with a minimum of discomfort. Patients *J Jo* and *B Cl*, with relatively high blood concentrations, experienced more severe reactions to the drug. Although the data are too few to be conclusive, they suggest that individual variations in the ability to absorb the drug or to remove it from the blood may determine the likelihood of reactions.

Comparison of blood concentrations attained with 200, 400, and 800 mg. doses (see figures 2 to 4) demonstrates a significant difference between the manner in

TABLE 5

Recovery from Urine of p-Formylacetanilide Thiosemicarbazone during 24 Hours after First of Two 200 Mg. Doses Administered Eight Hours Apart

PATIENT	MG. RECOVERED	PER CENT OF 400 MG. DOSE RECOVERED
J Mc	103	51.5
T Ob	140	70.0
A Le	123	61.5
T Ma	123	61.5

which this compound is handled by the body in dogs and humans. Burke and Titus (7) have found that dogs may rapidly develop tolerance to Myvizone so that increasingly large doses are required to maintain a constant concentration in the blood. In man this does not seem to be true; rather, there is suggestive evidence of some accumulation of the drug within the blood.

Therapeutic Effects

The patients studied in this series all had long-standing, far advanced pulmonary tuberculosis with extensive fibrosis and cavitation. Dramatic roentgenographic evidence of improvement in such lesions was not to be expected and was not seen during Myvizone therapy. Some improvement was detected in 5 of the 12 patients who were treated for more than a month (table 1). Two of the 12 patients were worse and the other 5 showed no change. The roentgenograms of one patient are presented in figure 5.

Symptomatic improvement, on the other hand, was prompt in that there was marked reduction in the frequency and severity of the cough, with a decrease in sputum production in all cases. Two patients (*J Mc*, *J Ro*) produced as much as 450 cc. of sputum daily prior to treatment; while receiving Myvizone

they expectorated less than 75 cc. daily. Cough and expectoration gradually increased when the medication was stopped.

None of the patients had a high fever initially and in none was there a prompt defervescence such as is seen with streptomycin.[3] The temperature fall which was noted in several of the men was most obvious in *J Mc*, whose course is summarized in figure 6. Another patient (*B Cl*) had a prolonged hemoptysis beginning on the fifteenth day of Myvizone therapy. Despite roentgenographic evidence of more extensive pulmonary involvement after the bleeding, his fever remained below 101°F. and he had minimal symptoms until the drug was discontinued forty days later. His temperature then rose to 102.6°F. and his symptoms became pronounced until medication was resumed, when the temperature fell

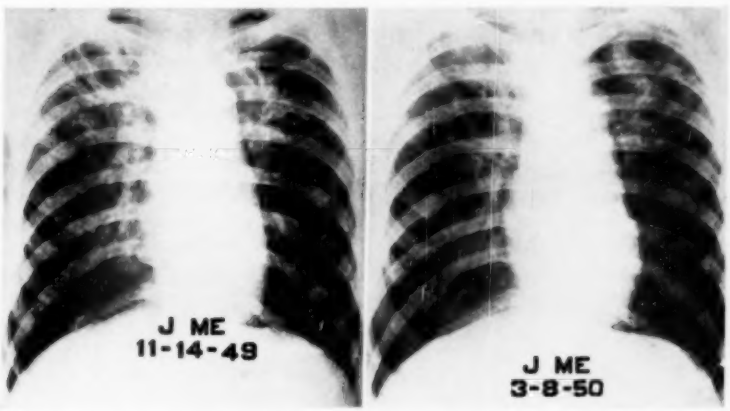

FIG. 5. Roentgenograms of patient *J Mc* before treatment (November 14, 1949) and after 108 days of Myvizone therapy (March 8, 1950). Prior to treatment the lesions were progressive. The clinical course of this 27-year-old white man is charted in figure 6.

promtly below 101°F. again. Myvizone was again stopped and there was subsequent evidence of spread of the disease as seen in the roentgenograms.

Most of the patients had a marked decrease in the number of acid-fast bacilli seen in smears of the sputum as well as a decreased volume of expectoration. In no instance did the sputum become persistently negative for acid-fast bacilli.

The erythrocyte sedimentation rate fell below the pretreatment level in all cases where therapy was continued for more than one week; in 7 cases there was no detectable sedimentation in one or more specimens examined during the course of therapy. There was no detectable correlation between the changes in sedimentation rate and other evidence of therapeutic effects of Myvizone. The rate fell

[3] Rapid defervescence was seen in a patient not included in this series. This 19-year-old Negro man with acute tuberculous pneumonia in the process of excavation was given 400 mg. of Myvizone daily. His pretreatment temperature of 102.2° F. fell to 99° F. within two days after the institution of therapy and promptly rose again when treatment was discontinued.

almost to zero in a few patients whose subsequent course made it unlikely that there was any corresponding improvement in the disease process. This supports the concept (3) that the sedimentation rate is of no prognostic significance during the course of Myvizone therapy.

Bacterial Sensitivity to Myvizone

The Myvizone sensitivity of the tubercle bacilli isolated prior to treatment and during two four-week periods of therapy ranged from less than 0.09 γ per ml. to 3.12 γ per ml. for the 35 specimens examined to date. Pretreatment cul-

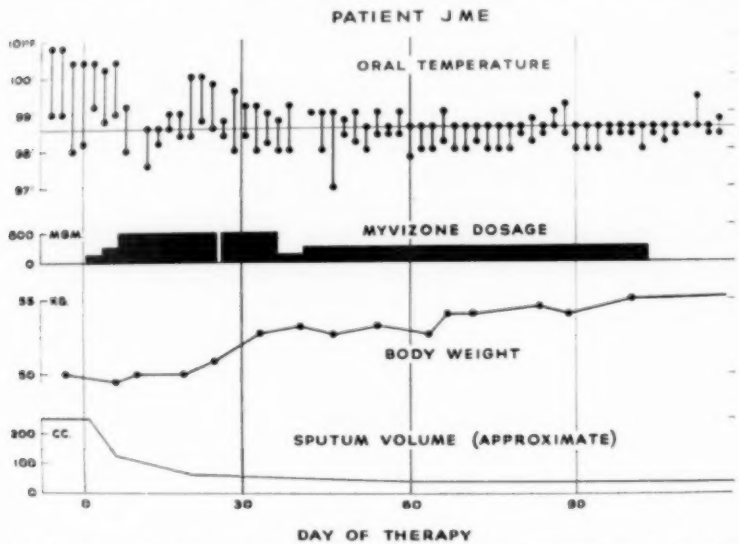

FIG. 6. Course of patient *J Me* during Myvizone therapy (see figure 5). Maximal and minimal temperatures are charted for each two-day period.

tures were not all equally sensitive to the agent and there was some variation in sensitivity during treatment. In one patient (*M Ca*) the cultures of tubercle bacilli apparently became more resistant; in three others (*B Cl, T Ob, V Pf*), more sensitive. The data are too few to allow an evaluation of the significance of these findings.

The sensitivity of the tubercle bacilli to streptomycin and *p*-aminosalicylic acid did not change significantly during Myvizone therapy.

COMMENT

Although Myvizone is appreciably toxic in the higher doses employed in this study, it seems that serious consequences may be minimized or avoided by certain precautions.

Careful evaluation of hepatic function should be made in each case prior to treatment, and at present detectable impairment should be considered a contraindication. The danger of treating patients with extensive amyloidosis has been pointed out by Schlaaff (10) and was demonstrated again in this study.

Treatment with daily dosages of 400 mg. or more should be undertaken with caution. Frequent examination of the peripheral blood and evaluation of the hepatic function should be performed while patients are on such a regimen.

At present treatment with daily doses of 200 mg. or less should be accompanied by frequent determinations of the leukocyte count and of the erythrocyte count or hemoglobin concentration. Repeated tests of hepatic function, such as the cephalin flocculation or thymol turbidity reactions, should be made. The appearance of malaise, listlessness, or similar symptoms should be considered cause for caution. Whenever definite evidence is obtained of hepatic dysfunction or severe hematologic abnormality, treatment should be interrupted or the dosage reduced.

All forms of toxic reactions encountered in this study were reversible except in the presence of pre-existing hepatic dysfunction. Improvement followed interruption of the Myvizone therapy or reduction in the dosage and in most instances treatment could be resumed uneventfully, usually at a lower dosage, after the reaction had subsided.

No conclusions can be drawn from this small series of patients as to the therapeutic efficacy of Myvizone other than that there is evidence that the drug has antituberculous activity. The reduction of cough and expectoration was consistent and contributed to the patients' comfort.

SUMMARY

1. *p*-Formylacetanilide thiosemicarbazone (Myvizone) possessed significant toxicity when administered orally over a period of several weeks. This toxicity was appreciably greater when daily doses of 400 mg. or more were given. The toxic reactions were reversible when the dose was reduced or the medication discontinued except in one instance where hepatic function was already impaired by amyloidosis.

2. The most frequent toxic reaction was a sensation of malaise, listlessness, or sleepiness. This symptom was noted by 13 of the 16 patients treated and, in 7, preceded more severe reactions by one to twelve days.

3. Nausea, vomiting, or both, were experienced by 11 patients and in 2 were so severe that Myvizone had to be interrupted.

4. Dermatitis occurred in 4 patients, 2 of whom had to discontinue treatment temporarily. Two other patients lost their sense of taste for the duration of therapy.

5. Abnormal results from tests of hepatic function were detected in 8 patients during the course of treatment. One patient whose liver function was already impaired by amyloidosis may have been made permanently worse by a short course of Myvizone.

6. Acute hemolytic anemia occurred in one patient who was receiving 800 mg.

of Myvizone daily; microcytic anemia occurred in 2 other patients during treatment. A slight to moderate decrease in the erythrocyte count and hemoglobin concentration was encountered in almost all other patients receiving larger doses. Granulocytopenia was not observed.

7. Absorption of Myvizone from the intestinal tract and removal of the drug from the blood were slow. Maximal concentrations of 0.6 to 1.0 γ per ml. were found three to five hours after oral administration of 200 mg. of the drug, and detectable quantities were still present twenty-four hours after medication. There was some evidence that accumulation occurs, blood concentrations of 5 to 11 γ per ml. being present when 800 mg. daily were administered chronically. The body may convert some of the compound to an aromatic amine by modifying or destroying the thiosemicarbazone moiety.

8. There was no consistent increase in the resistance of tubercle bacilli to Myvizone, streptomycin, or *p*-aminosalicylic acid when cultures were obtained during the first eight weeks of treatment with Myvizone alone.

9. No conclusions can be drawn as to the therapeutic efficacy of the compound from this small series of patients other than that it seems to have antituberculous activity. Cough and expectoration were uniformly reduced during treatment.

SUMARIO

Farmacología Humana de la Tiosemicarbazona de p-Formilacetanilida

(*Mivizona*)

1. Al ser administrada por vía oral durante un período de varias semanas, la tiosemicarbazona *p*-formilacetanilídica (Mivizona) reveló toxicidad significativa, más intensa cuando se suministraron dosis diarias de 400 mg. o más. Las reacciones tóxicas fueron reversibles cuando se rebajó la dosis o suspendió la medicación, salvo en un caso en que la función hepática estaba ya afectada por la amiloidosis.

2. La reacción tóxica más frecuente consistió en sensación de malestar, apatía o somnolencia, observando este síntoma 13 de los 16 enfermos tratados y precediendo en 7 de uno a doce días la aparición de reacciones más graves.

3. Once enfermos experimentaron náuseas o vómitos, o ambos, siendo en 2 tan intensos que hubo que interrumpir la Mivizona.

4. Sobrevino dermatitis en 4 pacientes, 2 de los cuales tuvieron que abandonar el tratamiento temporalmente. Otros dos enfermos perdieron el sentido del gusto mientras duró la terapéutica.

5. Durante el tratamiento, las pruebas de la función hepática dieron resultados anómalos en 8 pacientes. Un sujeto, cuya función hepática estaba ya afectada por la amiloidosis, puede haber quedado empeorado permanentemente tras una breve serie de Mivizona.

6. Durante el tratamiento, se presentó anemia hemolítica aguda en un enfermo, y microcitaria en otros dos. En caso todos los demás pacientes que recibieron dosis grandes, notóse baja leve a moderada de la fórmula eritrocitaria y de la concentración de hemoglobina. No se observó granulocitopenia.

7. La absorción de Mivizona en el tracto intestinal y la excreción de la droga de la sangre fueron lentas. De tres a cinco horas después de la administración oral de 200 mg. de la droga, descubriéronse concentraciones máximas de 0.6 a 1.0 γ por ml., y a las veinticuatro horas había todavía presentes cantidades apreciables. Hubo algunos signos de que ocurría acumulación, habiendo presentes concentraciones de 5 a 11 γ por ml. al administrarse crónicamente 800 mg. diarios. El organismo puede convertir parte del compuesto en amina aromática modificando o destruyendo la fracción tiosemicarbazónica.

8. No hubo aumento sistemático en la resistencia de los bacilos tuberculosos a la Mivizona, la estreptomicina o al ácido *p*-aminosalicílico cuando se obtuvieron los cultivos durante las primeras ocho semanas de tratamiento con la Mivizona sola.

9. No cabe sacar conclusiones relativas a la eficacia terapéutica del compuesto, de esta pequeña serie de enfermos, aparte de que parece poseer actividad antituberculosa. Durante el tratamiento disminuyeron invariablemente la tos y la expectoración.

Acknowledgments

The authors are exceedingly grateful to Dr. Elwood O. Titus of the Squibb Institute for Medical Research for determining the concentrations of *p*-formylacetanilide thiosemicarbazone and for assisting in the interpretation of these data.

The authors are deeply indebted to Miss Mollie Mollov, Senior Bacteriologist, Queens General Hospital, who performed the sensitivity tests reported here.

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THE EFFECT OF 4-ACETYLAMINOBENZAL THIOSEMICARBAZONE (TIBIONE) ON EXPERIMENTAL TUBERCULOSIS IN GUINEA PIGS[1]

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Investigations on the effectiveness of the thiosemicarbazones *in vivo* and *in vitro* have been reported recently by Domagk (1). The status of this form of chemotherapy in human tuberculosis has been reviewed by Mertens and Bunge (2). Their reports indicate that the thiosemicarbazones must be considered as important antituberculous agents.

The purpose of this paper is to report a study on the effect of 4-acetylaminobenzal acid (Tibione[2]) and Tibione combined with streptomycin on experimental tuberculosis in guinea pigs.

MATERIALS AND METHODS

Forty female guinea pigs weighing 325 to 375 gm. were observed under controlled conditions for normalcy, tuberculin-tested, and divided into equivalent groups of 10 each. Animals were housed five per six square feet, bedded in wood shavings, and fed on a purina chow supplemented with oats and daily greens. No water was given.

A previously grown culture[3] of H37Rv was weighed and emulsified under aseptic conditions so that 0.2 mg. dry weight was the infecting dose per animal. Injections were made subcutaneously over the sternum. This infecting site has the advantage of permitting observations on the course of the disease in each animal during the experiment.

Fourteen days post infection each animal was tuberculin-tested with 0.1 ml. of 5 per cent Old Tuberculin and all were found to be positive.

Two days later treatment for each group was started as follows:

Group I. Ten guinea pigs injected with saline

Group II. Ten guinea pigs injected with 50 mg. of 4-acetylaminobenzal thiosemicarbazone (Tibione)

Group III. Ten guinea pigs injected with 10 mg. of streptomycin hydrochloride base

Group IV. Ten guinea pigs injected with both 25 mg. of Tibione and 5 mg. of streptomycin hydrochloride base.

In each group above, the given agent was diluted to be contained in a 1.0 ml. volume and was injected subcutaneously in the dorsum daily during twenty-eight consecutive days.

[1] From the Division of Tuberculosis and Division of Pathology, Grasslands Hospital; and Department of Laboratories and Research of Westchester County, Valhalla, New York.

[2] The Tibione used in this study was supplied by Schenley Laboratories, Inc., New York, New York.

[3] Obtained from Mr. W. Steenken, Jr., National Culture Bank, Trudeau Foundation, Saranac Lake, New York.

Daily observations of the infection site were made. The size, degree of localization, and time of ulceration were noted. Tuberculin tests were repeated at the end of treatment and one-half of the number of animals per group was sacrificed from each group. The remaining animals were continued under observation without treatment for an additional fourteen days, tuberculin-tested, and sacrificed as above. Each animal was weighed prior to sacrifice. Complete autopsies were performed with particular attention to the site of inoculation, axillary lymph nodes, mediastinal lymph nodes, spleen, liver, and lungs. Gross and microscopic observations were recorded. These recordings were made in accordance with the scheme of Feldman and Hinshaw (3), modified to suit the situation in hand. Moreover, in this modified scheme the size, degree of caseation, and number of lymph nodes involved are also recorded. The weights of the animals before and after treatment were recorded.

TABLE 1

Character of Inoculation Site

GROUP	NUMBER OF ANIMALS	TIME OF APPEARANCE AND NUMBER OF NODULES NOTED POST INFECTION	ULCERATION OF NODULE
Group 1. Saline-treated	10	20 to 24 days in 10 guinea pigs	8
Group 2. Tibione, 50 mg. subcutaneously daily (30 days)	10*	32 to 34 days in 3 guinea pigs	0
Group 3. Streptomycin HCl, 10 mg. subcutaneously daily (30 days)	10†	30 to 32 days in 8 guinea pigs	0
Group 4. Streptomycin HCl, 5 mg.; Tibione, 25 mg. daily (30 days) (both drugs administered subcutaneously)	10	32 to 34 days in 4 guinea pigs	0

* One animal died on the forty-third day of infection.

† One animal died on the forty-first day of infection.

Cultures for tubercle bacilli were made from the spleens at the time of sacrifice; white blood cell counts were also made.

RESULTS

The comparative findings among the four groups of animals treated as described are presented in figures 2 and 3.

Observations of the site of infection: The nodules of the site of infection appeared appreciably earlier in the saline-injected controls (Group I) than in the other groups (table 1). In addition, the nodules were more numerous, in that all control pigs developed nodules whereas only 3 Tibione-(Group II) and 4 Tibione-streptomycin (Group IV)—treated animals developed nodules. In this respect the Tibione group showed up to better advantage than the streptomycin-treated group (Group III), in that in the latter group 8 of 10 animals developed nodules (figures 2 and 3). The nodules in the control animals measured in almost all instances more than 0.5 cm. in diameter, were caseous and, in 8 instances, ulcer-

ated. The few nodules which were present in all other groups were much smaller and were not ulcerated.

Observations on the extent of tuberculous involvement: All animals were sacrificed at such time as to preclude any significant pulmonary involvement. This was done so that the duration of the experiment would parallel the work of Domagk. For this reason the 50 mg. dose of Tibione was also used.

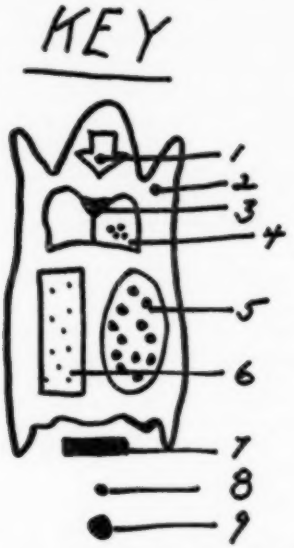

FIG. 1. Schematic representation showing key of symbols indicating extent of tuberculous lesions of guinea pigs seen at necropsy (modified by authors from Feldman, W. H., and Hinshaw, H. C. (3)).

Key: 1. Lesion over sternum at site of inoculation
2. Involvement of axillary lymph nodes
3. Involvement of mediastinal lymph nodes
4. Involvement of lungs
5. Nodular tuberculosis of spleen
6. Miliary tubercles in liver
7. Animal died days
8. Small lesion
9. Large lesion

The extent of involvement was graded on the basis of size and involvement of inoculation site, size, number, and degree of caseation of axillary and mediastinal lymph nodes involved, and extent of involvement of such organs as the liver and spleen (figures 1, 2, and 3).

The control saline-injected pigs exhibited moderate to marked involvement of the spleen in every instance, minimal liver lesions, and bilateral moderate-

sized lymph nodes with varying degrees of caseation. The members of this group sacrificed fourteen days after cessation of saline injection showed, in addition, moderate involvement of the mediastinal lymph nodes in 4 of 5 pigs; 3 of these contained caseous foci.

The Tibione-treated group of pigs did not show any liver or splenic involvement, and in only 2 instances was there tuberculous involvement of the axillary lymph nodes. None of the animals had any mediastinal lymph node involvement.

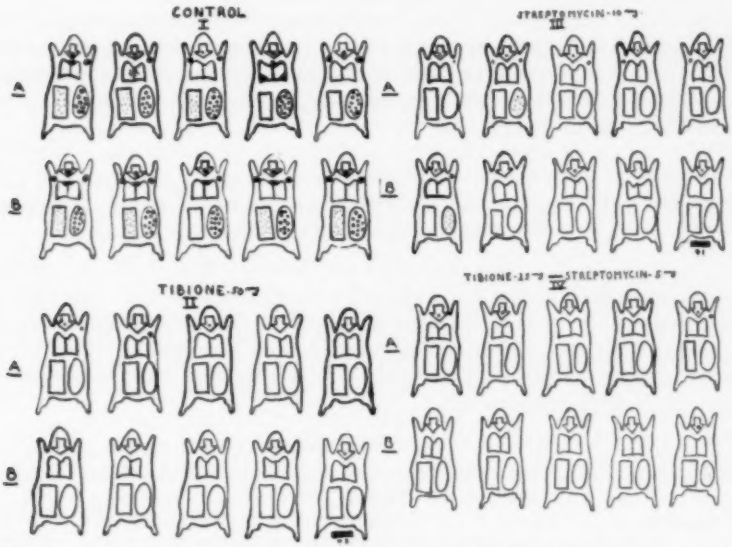

FIG. 2. (Left) Schematic representation of degree and type of involvement of control group (I) and Tibione-treated group (II). (A) represents animals sacrificed immediately after cessation of therapy; (B) represents animals sacrificed fourteen days after cessation of therapy.

FIG. 3. (Right) Schematic representation of degree and type of involvement of streptomycin group (III) and Tibione-streptomycin—treated group (IV). (A) represents animals sacrificed immediately after cessation of therapy; (B) represents animals sacrificed fourteen days after cessation of therapy.

The streptomycin-treated group showed minimal involvement of the spleen in 2 instances and axillary lymph node involvement in 5 instances.

The Tibione-streptomycin—treated group had no liver or spleen involvement with the exception of a few nodules in one spleen. In only one animal did an axillary node show tuberculosis.

Other observations: The Tibione-treated animals did not gain weight to the same extent as the other groups. While under treatment their average weight gain was 150 gm. less than the other group at the time of cessation of therapy.

In those that were kept alive for fourteen days following cessation of therapy the weight gain was rapid.

White blood cell counts did not reveal any significant differences between the groups. Cultures for tubercle bacilli from the spleens of the Tibione- and Tibione -streptomycin—treated animals were all negative. Histologic examination of liver and kidney did not show any evidence of toxic change.

SUMMARY

In the limited type of experiment performed and with the dosage as employed, 4-acetylaminobenzal thiosemicarbazone (Tibione) proved to be as effective an agent against tuberculosis in guinea pigs as streptomycin. Combined therapy with Tibione and streptomycin in one-half of the dose employed, as when either drug was used alone, was equally effective as Tibione alone and possibily more effective than streptomycin alone.

SUMARIO

El Efecto de la Tiosemicarbazona 4-Acetilaminobenzálica (Tibiona) sobre la Tuberculosis Experimental del Cobayo

En la limitada clase del experimento ejecutado y con la dosis empleada, la tiosemicarbazona 4-acetilaminobenzálica (Tibiona) se mostró tan eficaz como la estreptomicina contra la tuberculosis en el cobayo. Una terapéutica combinada de Tibiona y estreptomicina, a la mitad de la dosis empleada al utilizar una u otra por sí sola, resultó igual en eficacia a la Tibiona sola y posiblemente más eficaz que la estreptomicina sola.

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THE EFFECT OF DIHYDROSTREPTOMYCIN—PARA-AMINOSALICYLATE (DHS–PAS) ON EXPERIMENTAL TUBERCULOSIS IN GUINEA PIGS[1]

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(Received for publication February 14, 1950)

INTRODUCTION

In a previous paper (1) the writers reviewed briefly the reports of other workers and presented their own data which indicate that in experimental tuberculosis the therapeutic effect of combined treatment with streptomycin and para-aminosalicylic acid (PAS) is greater than that produced by either drug alone. It has been reported (2) that streptomycin and PAS may be administered together as a PAS salt of streptomycin containing 56 per cent streptomycin and 44 per cent PAS. It has also been reported (2) that this salt is superior to streptomycin alone in experimental tuberculosis in mice, in that it increases the survival time. There is evidence that the chemical union of streptomycin and PAS does not interfere with the activity of streptomycin and that, when the PAS-streptomycin compound is given intramuscularly to patients, the two portions of the salt may act independently, as determined by studies on concentrations in the blood (3).

The present report describes an experiment to test the efficacy of a similar salt, dihydrostreptomycin—para-aminosalicylate (DHS-PAS)[2], in experimental tuberculosis in guinea pigs and to learn whether the salt is superior to dihydrostreptomycin alone in causing regressive changes in an actively progressing tuberculous disease. The compound used contained 59 per cent dihydrostreptomycin and 41 per cent PAS.

METHOD

Each of 90 male guinea pigs of an average weight of 600 to 700 gm. was inoculated subcutaneously over the sternum with 0.1 mg. (moist weight) of a 25-day-old culture of virulent human-type tubercle bacilli (H37Rv strain). Twenty-one days later 6 of the animals were killed and were found to have grossly visible lesions at the site of inoculation, the axillary lymph nodes, and in the liver and spleen. Subsequent histologic examination disclosed active pulmonary lesions as well.

The remaining 84 animals were divided into eight groups, as shown in figure 1. Treatment started on the twenty-first day of infection and continued for sixty-two days. All of the surviving animals were then killed and a record was made of the extent of disease observed. Portions of spleen, liver, lungs, tracheobronchial lymph nodes, site of inoculation, and one axillary lymph node were preserved for histopathologic examination. A portion of each spleen was cultured for tubercle bacilli. The cultures eventually were tested for any increased resistance to dihydrostreptomycin and to PAS.

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[1] From the Division of Experimental Medicine, Mayo Foundation, Rochester, Minnesota.

[2] The dihydrostreptomycin—para-aminosalicylate was furnished through the courtesy of Parke, Davis & Company, Detroit, Michigan.

The treatment regimens used were based on previous experience. It has been shown that a daily dose of 6 mg. of streptomycin (4) or dihydrostreptomycin (5) has a definite deterrent action on actively progressing tuberculosis in guinea pigs. This amount of dihydrostreptomycin was, therefore, selected to treat one group of animals (group 2), and 10.17 mg. of DHS-PAS (which contains 6 mg. of dihydrostreptomycin and 4.17 mg. of PAS) were used to treat another group (group 5). One group (group 4) was treated with 4.17 mg. of PAS alone, given in 5.8 mg. of the sodium salt (NaPAS).[1]

It was expected that a daily dose of 6 mg. of dihydrostreptomycin would result in such marked regression and repair of the lesions that any increased beneficial effect of using 10.17 mg. of DHS-PAS would possibly be difficult to measure. For this reason, a group of animals (group 3) was treated with 2 mg. of dihydrostreptomycin for comparison with a group (group 6) treated with 3.39 mg. of DHS-PAS which contains 2 mg. of dihydrostreptomycin. It has been shown that a daily dose of 2 mg. of streptomycin is only partially effective, as compared to a daily dose of 6 mg., in changing an active tuberculous infection in guinea pigs to one in which the signs of regression and healing predominate (6). It was expected that any additional benefit due to the PAS portion of the DHS-PAS salt could be detected by comparing the results obtained with 2 mg. of dihydrostreptomycin with those produced by 3.39 mg. of DHS-PAS.

Previous experience indicated that the small dose of sodium para-aminosalicylate (NaPAS) given to animals in group 4 probably would be ineffective in producing any demonstrable favorable change, but that the administration of 100 mg. of NaPAS would result in a definite, although partial, retardation of the tuberculous process (7). Groups 7 and 8 were added to this experiment to learn whether the parenteral administration of subeffective amounts of dihydrostreptomycin and NaPAS would produce a result superior to that achieved by either drug alone, as is the case when PAS is given in the diet (1).

Each of the various doses was given once daily in 1 ml. amounts of solution injected into the axillary space. An exception was made for the animals given 100 mg. of NaPAS which, because of the severe local irritation, was injected once daily in 0.5 ml. amounts alternately in the inguinal and axillary spaces.

RESULTS

Too few animals in each group died during the course of the experiment to permit evaluation of the death rates. Except where the lesions of tuberculosis were widespread, the cause of death of those that died was not apparent.

The extent of the disease seen in each animal at the time of necropsy is schematically presented in figure 1. It is seen that in comparison to the untreated group (group 1), the animals treated with 6 mg. of dihydrostreptomycin daily and those given 10.17 mg. of DHS-PAS had very little evidence of tuberculosis. There are too few visible lesions in either of these groups to make a satisfactory comparative evaluation possible. With these doses any beneficial effect of the DHS-PAS over dihydrostreptomycin alone may have been masked by the excel-

[1] Furnished through the courtesy of Cilag, Ltd., Schaffhausen, Switzerland.

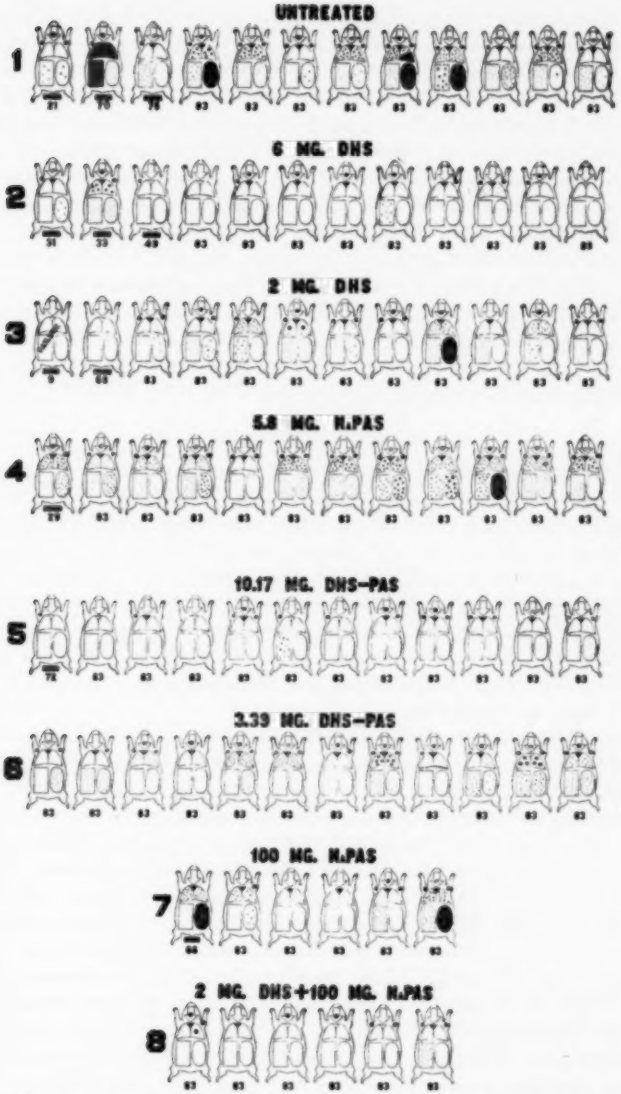

FIG. 1. Schematic representation of the extent of tuberculosis seen when the animals were examined after sixty-two days of treatment, which started twenty-one days after infection. The black bar indicates death of the animal before the end of the experiment. The numerals indicate the number of days of infection. The rectangle represents the liver and the oval figure represents the spleen. The arrow indicates the site of inoculation and the black dot or circle within it represents an abscess and ulcer, respectively.

lent result achieved by 6 mg. of dihydrostreptomycin given alone. The administration of 5.8 mg. of NaPAS alone (4.17 mg. of PAS) had no apparent favorable effect on the disease.

The observations at necropsy revealed that the administration of 2 mg. of dihydrostreptomycin (group 3) did result in less extensive disease than that seen in the untreated animals, but the results are inferior to those achieved by 6 mg. of dihydrostreptomycin and by 10.17 mg. of DHS-PAS. The extent of the disease in the animals treated with 3.39 mg. of DHS-PAS (group 6) is comparable to that seen in the animals treated with 2 mg. of dihydrostreptomycin, indicating that the use of 3.39 mg. of the salt did not produce a result more favorable than that achieved by the use of 2 mg. of dihydrostreptomycin alone.

The number of animals in groups 7 and 8 is too small for critical analysis, but it appears that the administration of 100 mg. of NaPAS retarded the disease and, when it was used with 2 mg. of dihydrostreptomycin, there was a more favorable effect than was produced by either drug alone in these doses.

Histopathologic Aspects

Microscopic examination confirmed the observations made at necropsy. There was striking evidence of resolution and healing in the lungs, liver, and spleens of animals treated with 6 mg. of dihydrostreptomycin (group 2), 10.17 mg. of DHS-PAS (group 5), and in those treated with 100 mg. of NaPAS plus 2 mg. of dihydrostreptomycin (group 8). Most of the residual lesions consisted of fibrotic areas which could not be identified as having previously been active tuberculous processes. In the parenchymal organs of a few animals in these groups there were occasional small collections of epithelioid cells with no necrosis. However, the tracheobronchial lymph nodes, the site of inoculation, and the axillary lymph nodes did have active necrotic foci.

Treatment with 2 mg. of dihydrostreptomycin (group 3) and with 3.39 mg. of DHS-PAS (group 6) inhibited the disease. Instead of the disseminating lesions with extensive necrosis seen in the untreated controls, the lesions consisted largely of large collections of epithelioid cells and giant cells with small necrotic centers. Treatment with 5.8 mg. of NaPAS (group 4) produced no microscopically demonstrable beneficial effect. Two of the 6 animals treated with 100 mg. of NaPAS (group 7) had only slight evidence of regressive changes and the other 4 had lesions comparable to those treated with 2 mg. of dihydrostreptomycin.

An average index of infection for each group based on the histologic character of the lesions in each animal is presented in table 1 (8). In this method of evaluation the active progressive lesions are given values of 10 or more depending on the extent of involvement, and the inactive lesions are given values of 1 to 3. A comparison of the data thus obtained indicates that the administration of 10.17 mg. of DHS-PAS was not superior to 6 mg. of dihydrostreptomycin in its capacity to cause a reversal and healing of the tuberculous processes. There is no evidence that the administration of 3.39 mg. of DHS-PAS produced an effect more favorable than that achieved by 2 mg. of dihydrostreptomycin alone.

Bacteriologic Studies

All cultures isolated from the treated as well as the untreated animals were found to be sensitive *in vitro* to 1.0 γ of dihydrostreptomycin per ml. of egg yolk agar and to 0.072 mg. of PAS per 100 ml. of egg yolk agar, as determined by methods previously described (9, 10). This is the same as found for the culture used to infect the animals.

TABLE 1

Average Severity of Tuberculosis Expressed Numerically, Based on Histopathologic Characteristics

GROUP NUMBER	TREATMENT (DAILY)	ANIMALS, NUMBER	SPLEEN (MAX.: 35)	LUNGS (MAX.: 30)	LIVER (MAX.: 25)	SITE OF INOCULATION (MAX.: 10)	AVERAGE INDEX OF INFECTION (MAX.: 100)
1	None	11*	24.0	17.7	18.7	10.0	70.4
2	6 mg. DHS†	12	1.6	8.0	1.5	7.5	18.6
3	2 mg. DHS	11*	7.5	7.4	6.2	9.0	30.1
4	5.8 mg. NaPAS‡	11*	21.3	22.4	18.6	10.0	72.3
5	10.17 mg. DHS-PAS§	12	3.0	7.0	1.0	8.0	19.0
6	3.39 mg. DHS-PAS	12	10.1	7.3	6.0	9.0	32.4
7	100 mg. NaPAS	6	10.1	7.3	6.0	9.0	32.4
8	2 mg. DHS plus 100 mg. NaPAS	6	1.0	5.0	2.0	8.0	16.0

* Tissues from 1 animal of the original 12 not available for histopathologic examination.
† DHS = dihydrostreptomycin.
‡ NaPAS = sodium para-aminosalicylate.
§ DHS-PAS = dihydrostreptomycin—para-aminosalicylate.

COMMENT

To detect any therapeutic advantage in the use of two or more antituberculous agents concomitantly in an experimental infection, it is imperative that the dose of each drug be sufficiently low so that the final result cannot be attributed to either of the agents alone (1, 5). For example, the marked degree of regression and healing produced by the administration of 6 mg. of dihydrostreptomycin alone was so great that any added beneficial effect of the 10.17 mg. of DHS was not demonstrable. The strikingly favorable results produced by the 10.17 mg. of DHS-PAS can be attributed solely to the 6 mg. of dihydrostreptomycin which it contains. If the salt, DHS-PAS, had a greater antituberculous potential in guinea pigs than dihydrostreptomycin, it would be expected that a daily dose of 3.39 mg. would produce a beneficial effect greater than the incomplete regression of the disease caused by 2 mg. of dihydrostreptomycin. However, the effect of 3.39 mg. of DHS-PAS was not demonstrably superior to the effect of 2 mg. of dihydrostreptomycin alone.

Although 10.17 mg. of DHS-PAS did cause a very marked regression and healing of the lesions, the small amount of PAS which it contains was found to

be ineffective when administered alone as NaPAS. It required 100 mg. of NaPAS (equivalent to 72 mg. of PAS) to produce an effect even comparable to that achieved by 2 mg. of dihydrostreptomycin. To administer this much PAS parenterally as the salt, DHS-PAS, it would be necessary to give each guinea pig 175.6 mg. The failure of the salt, DHS-PAS, to cause detectable beneficial changes in the disease superior to those caused by dihydrostreptomycin alone may be due to the lack of effect of the small amount of PAS in the salt.

SUMMARY AND CONCLUSIONS

An experiment was performed to test the efficacy of dihydrosteptomycin-para-aminosalicylate (DHS-PAS) in experimental tuberculosis of guinea pigs and to compare its effect with an equivalent amount of dihydrostreptomycin. The salt, DHS-PAS, contained 59 per cent dihydrostreptomycin and 41 per cent PAS. Guinea pigs were infected with 0.1 mg. of virulent human tubercle bacilli (strain H37Rv), and twenty-one days later were divided into groups and treated once daily for sixty-two days as follows: (*1*) no treatment (controls); (*2*) 6 mg. of dihydrostreptomycin; (*3*) 2 mg. of dihydrostreptomycin; (*4*) 5.8 mg. of NaPAS; (*5*) 10.17 mg. of DHS-PAS, which is equivalent to 6 mg. of dihydrostreptomycin and 5.8 mg. of NaPAS; (*6*) 3.39 mg. of DHS, which is equivalent to 2 mg. of dihydrostreptomycin; (*7*) 100 mg. of NaPAS; and (*8*) 100 mg. of NaPAS plus 2 mg. of dihydrostreptomycin.

The results of necropsy and histopathologic study indicated that DHS-PAS in the doses used was comparable to dihydrostreptomycin in its effect on the disease. There was no evidence of superiority of DHS-PAS over dihydrostreptomycin alone. The small amount of PAS in 10.17 mg. of DHS-PAS had no demonstrable effect on the disease when given alone as 5.8 mg. of NaPAS. A daily dose of 100 mg. of NaPAS resulted in only partial regression of the disease but, when used in combination with 2 mg. of dihydrostreptomycin, the result was comparable to that caused by 6 mg. of dihydrostreptomycin or 10.17 mg. of DHS-PAS.

It is concluded that dihydrostreptomycin—para-aminosalicylate is as effective as, but not superior to, dihydrostreptomycin in experimental tuberculosis in guinea pigs.

SUMARIO

El Efecto de la Dihidroestreptomicina-Para-Aminosalicilato (DHS-PAS) sobre la Tuberculosis Experimental del Cobayo

En un experimento se comprobó la eficacia de la dihidroestreptomicina-para-aminosalicilato (DHS-PAS) en la tuberculosis experimental del cobayo y se comparó el efecto con el producido por una dosis equivalente de dihidroestreptomicina. La sal, DHS-PAS, contenía 59 por ciento de dihidroestreptomicina y 41 por ciento de PAS. Los cobayos fueron infectados con 0.1 mg. de bacilos tuberculosos humanos virulentos (cepa H37 Rv), siendo divididos veintiún días después en grupos y tratados una vez al día en la forma siguiente: (*1*) sin tratamiento

(testigos); (*2*) 6 mg. de dihidroestreptomicina; (*3*) 2 mg. de dihidroestreptomicina; (*4*) 5.8 mg. de NaPAS; (*5*) 10.17 mg. de DHS-PAS representando 6 mg. de dihidroestreptomicina y 5.8 mg. de NaPAS; (*6*) 3.39 mg. de DHS representando 2 mg. de dihidroestreptomicina; (*7*) 100 mg. de NaPAS; y (*8*) 100 mg. de NaPAS más 2 mg. de dihidroestreptomicina.

Los resultados de la autopsia y del estudio histopatológico indicaron que, en su efecto sobre la enfermedad, la DHS-PAS era comparable, a las dosis utilizadas, a la dihidroestreptomicina, sin mostrar signos de superioridad sobre la última. La pequeña proporción de PAS en 10.17 mg. de DHS-PAS no ejerció efecto demostrable sobre la enfermedad cuando se administró por sí sola en forma de 5.8 mg. de NaPAS. Una dosis diaria de 100 mg. de NaPAS sólo logró regresión parcial de la dolencia, pero combinada con 2 mg. de dihidroestreptomicina, dió resultado comparable al obtenido por 6 mg. de dihidroestreptomicina o 10.17 mg. de DHS-PAS.

La deducción es que la dihidroestreptomicina-para-aminosalicilato es tan eficaz como, pero no superior a, la dihidroestreptomicina en la tuberculosis experimental del cobayo.

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THE INABILITY OF *p*-AMINOSALICYLIC ACID TO DELAY THE EMERGENCE OF STREPTOMYCIN-RESISTANT TUBERCLE BACILLI IN MICE[1,2]

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INTRODUCTION

Graessle and Pietrowski (1) have reported that the addition of relatively low concentrations of *p*-aminosalicylic acid (PAS) to streptomycin prevents or greatly retards the development *in vitro* of streptomycin-resistant tubercle bacilli.

Karlson and his associates (2) isolated, after three months of treatment, streptomycin-resistant tubercle bacilli from one of 14 patients treated with streptomycin in combination with either PAS or with both PAS and Promin. Four of these patients were found to harbor streptomycin-resistant tubercle bacilli at the end of six months of combined therapy. This was less than the expected incidence of streptomycin-resistant tubercle bacilli in patients treated with streptomycin alone.

Dunner and co-workers (3) treated 26 patients with both streptomycin and PAS and isolated streptomycin-resistant tubercle bacilli from only 12 per cent at 60 days; 16 per cent at 90 days; and 42 per cent at 120 days. As compared with patients receiving streptomycin alone, these findings suggested a delay in the emergence of streptomycin-resistant tubercle bacilli.

The combined data on emergence of streptomycin-resistant tubercle bacilli given at the Veterans Administration Seventh Streptomycin Conference (4) indicated that "the total incidence of resistant specimens obtained in groups of patients receiving PAS in conjunction with streptomycin was no greater than the incidence of resistant specimens among the pretreatment series."

If confirmed, these observations obviously would be of great importance for the streptomycin therapy of tuberculosis.

Recently the present writers reported (5) that streptomycin-resistant tubercle bacilli could be isolated from a majority of mice infected with streptomycin-sensitive tubercle bacilli and treated for prolonged periods with streptomycin. This finding suggested a method for determining the effect of combined therapy on the emergence of streptomycin-resistant tubercle bacilli *in vivo*.

The present report concerns itself with the effect of PAS on the development of streptomycin-resistant tubercle bacilli in mice.

METHODS

One hundred mice[3] weighing from 18 to 22 gm. were divided at random into groups of 20 and were infected intravenously with 0.1 mg. wet weight of a suspension of *Mycobacterium tuberculosis var. hominis* (H37Rv).

[1] From the Department of Bacteriology, Northwestern University Medical School, Chicago, Illinois.

[2] This investigation was supported (in part) by a research grant from the National Institutes of Health, Public Health Service.

[3] Strong A strain.

The mice were then treated in the following manner, starting with the same day they were infected. Twenty mice received 1.5 mg. of streptomycin subcutaneously, given twice daily in doses of 0.75 mg. at each injection; 20 mice received 1.5 mg. of streptomycin plus PAS administered in the diet in a concentration of 0.25 per cent; 20 mice received 1.5 mg. of streptomycin plus 0.5 per cent of PAS in the diet; 20 mice received 1.5 mg. of streptomycin plus 1.0 per cent of PAS in the diet; and 20 mice received neither streptomycin nor PAS.

The treatments were continued for a period of 183 days (six months) at which time all surviving animals were sacrificed. At the time of death or at the time the mice were sacrificed, one lung was removed and cultured for tubercle bacilli by a previously described method (5). Lung specimens were obtained from all but 3 mice. When sufficient growth was present, these cultures of tubercle bacilli were tested for their sensitivity to streptomycin by culturing on egg yolk nutrient agar medium containing twofold dilutions of streptomycin which varied from

TABLE 1

The Development of Resistance to Streptomycin of Tubercle Bacilli in Mice Treated with Streptomycin Alone and Streptomycin in Combination with Para-aminosalicylic Acid

NUMBER OF MICE	TREATMENT		NUMBER DEAD	NUMBER SACRIFICED	AVERAGE* SURVIVAL TIME	NUMBER OF MICE HAVING CULTURES RESISTANT TO STREPTOMYCIN	PER CENT OF MICE HAVING STREPTOMYCIN-RESISTANT CULTURES
	Streptomycin	PAS					
					Days		
20	1,500 γ	—	4	16	155.3	11	55.0
18	1,500 γ	0.25 per cent	5	13	170.8	8	44.4
20	1,500 γ	0.5 per cent	4	16	166.0	16	80.0
19	1,500 γ	1.0 per cent	9	10	160.0	11	57.9
20	—	—	20	0	44.4	0	0.0

* Calculated on the assumption that those mice sacrificed survived 183 days.

100 γ of streptomycin per ml. to 0.078 γ of streptomycin per ml. The sensitivity of each culture to streptomycin was recorded in terms of the least amount of streptomycin which completely inhibited growth.

The sensitivity to PAS of all of the cultures obtained from mice and treated with PAS also was tested by growing the tubercle bacilli in the same basal medium to which have been added suitable concentrations of PAS.

RESULTS

In table 1 is shown the incidence of streptomycin-resistant tubercle bacilli isolated from the lungs of mice receiving combined streptomycin and PAS therapy. In this study no cultures were considered resistant unless they grew on a medium containing at least 6.25 γ of streptomycin per ml. Growth of all cultures from the untreated control animals was uniformly completely inhibited by 3.12 γ or less.

It is apparent that there was no significant difference in the occurrence of

streptomycin-resistant tubercle bacilli among animals receiving streptomycin alone and those receiving streptomycin and PAS.

Although there was no significant difference between the number of resistant cultures isolated from the various groups of mice, the possibility was considered that the degree of resistance to streptomycin might have been higher for those cultures isolated from the animals treated with streptomycin alone.

That there was a tremendous variation in the sensitivity of the cultures to streptomycin is shown in table 2. There was, therefore, no significant difference in the degree of sensitivity to streptomycin between cultures from the groups of animals treated with streptomycin alone and those treated with streptomycin plus PAS.

None of the cultures tested showed any evidence of a decreased sensitivity to PAS.

TABLE 2

The Sensitivity to Streptomycin of Tubercle Bacilli Isolated from Mice Treated with 1,500 Micrograms of Streptomycin Daily and Various Amounts of PAS

CONCENTRATION OF STREPTOMYCIN IN MEDIUM	PER CENT CONCENTRATION OF PAS IN DIET			
	0.0	0.25	0.5	1.0
	Number of Cultures			
γ per ml.				
1.56	4	0	1	1
3.12	3	5	1	2
6.25	2	5	2	5
12.5	0	4	11	7
25.0	4	0	2	2
50.0	1	1	1	1
>100.0	6	3	2	1

COMMENT

These findings do not conform with those obtained *in vitro* (1) nor with the observations reported on patients treated with streptomycin and PAS (2, 3, 4). The reason for the discrepancy is not apparent unless the relatively long treatment period served to obscure differences in the rate of emergence of streptomycin-resistant tubercle bacilli. This long period of therapy was necessary because of the slow rate at which streptomycin-resistant tubercle bacilli appear in mice treated with streptomycin. Furthermore, it cannot be assumed that PAS would affect the emergence of streptomycin-resistant tubercle bacilli in mice in the same manner or to the same degree as it would *in vitro* or in human beings.

SUMMARY

In the number of mice harboring streptomycin-resistant tubercle bacilli, no significant difference was found between those treated with streptomycin alone and those treated with a combination of streptomycin and PAS. No increase was detected in the resistance of the cultures to PAS.

SUMARIO

La Incapacidad del Acido p-Aminosalicílico para Demorar la Aparición de Bacilos Tuberculosos Estreptomicinorresistentes en los Ratones

En lo tocante al número de ratones que albergan bacilos tuberculosos estreptomicinorresistentes, no se observó mayor diferencia entre los tratados con estreptomicina sola y con una combinación de estreptomicina y PAS. No se descubrió aumento en la resistencia de los cultivos al PAS.

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THE CLINICAL TOXICITY OF SULPHETRONE[1]

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Sulphetrone,[2] a derivative of diaminodiphenylsulfone, has been stated by English investigators (1-7) to be relatively nontoxic and to exert a considerable antituberculous effect. In guinea pigs, significant toxic reactions could not be detected, and the survival time of tuberculous animals was increased by the administration of this drug in rather large doses. The clinical reports varied in enthusiasm. Anderson and Strachan (5) treated 100 patients suffering from various forms of tuberculosis, and reported "40 per cent definite improvement." Madigan (6) claimed that exudative phases were "halted and reversed" by Sulphetrone in 70 cases. Clay and Clay (7) regarded the drug as an adjuvant at best and not a specific for tuberculosis. All these papers minimized the toxicity of the drug.

Observations

Animal experiments

Sulphetrone became available at Olive View Sanatorium late in 1948. A series of rabbits were inoculated intravenously with 0.01 mg. of a virulent bovine culture of tubercle bacilli. The untreated control animals showed extensive tuberculosis of the lungs, liver, spleen, and kidneys. Rabbits given Sulphetrone orally, Promin intravenously, para-aminosalicylic acid intramuscularly, or Promizole orally, 1 gm. each, daily, all showed similar but less extensive lesions. A rabbit treated with streptomycin, 200 mg. once a week, showed only half as much tuberculosis as the controls. Rabbits given combinations of Sulphetrone or other sulfones with streptomycin in similar dosage showed even less tuberculosis, consisting of only a few fine nodules in the kidneys and lungs.

Guinea pigs were infected subcutaneously with 0.01 mg. of the virulent human-type culture of tubercle bacilli, B88, and cages of 5 each were given different treatments. The control, untreated guinea pigs developed extensive caseous tuberculosis of lymph nodes, liver, spleen, and lungs, averaging 6 units of tuberculosis on the scale used here (11). Those treated with 40 mg. of streptomycin, once weekly, showed lesions only half as extensive, averaging 3 units of tuberculosis per guinea pig. Those given 1 gm. doses, orally, daily, of Sulphetrone, Promizole, Promin, or para-aminosalicylic acid alone, showed slightly more disease, averaging 4 units of tuberculosis apiece. Guinea pigs given combinations of these chemicals with streptomycin had lesions confined to the lymph nodes and averaged only 2 units of tuberculosis per pig. Repetition of this experiment yielded similar results. Sulfones were much less effective than streptomycin alone, but the combinations of streptomycin and sulfones were

[1] From Olive View Sanatorium, Olive View, California.

[2] A registered name for tetrasodium 4:4-bis(γ-phenyl-propylamino)-diphenylsulfone-α:γ:α:γ-tetrasulfonate, supplied by Burroughs, Wellcome and Co.

more effective than either alone. The only toxic effect due to Sulphetrone noted was enlargement and cyanosis of the spleen.

CLINICAL ADMINISTRATION

In view of these results and of the papers that had been published on Sulphetrone, it was considered appropriate to attempt a limited clinical investigation with this agent. Accordingly, over a period of eight months, 20 women ranging in age from 21 to 55 years, with various forms of tuberculosis, were given the drug. All of these patients had far advanced pulmonary disease and 5 of them had had recent "spreads." The series included 2 cases of endobronchial tuberculosis, one of pleural effusion, one of tuberculous empyema, 3 of tuberculous enteritis, one of sacro-iliac disease and cold abscess, and one of hematogenous tuberculids. A course of four months' therapy was arbitrarily chosen, but many patients were unable to tolerate the drug for that length of time; so the time decided on was four days to twenty weeks.

Sulphetrone was administered in 0.5 gm. tablets three times a day after meals. The initial dosage was thus 1.5 gm. per day. The hemoglobin and Sulphetrone concentrations of the blood were measured once a week.

An attempt was made to increase the daily dose by small increments every week and to add an evening dose in order to obtain a fasting concentration in the blood of 5 to 8 mg. per 100 cc., but this objective was seldom accomplished for any prolonged period of time.

Hemoglobin determinations were performed with a photoelectric technique and a scale of 100 per cent for 16 gm. Since anemia occurred regularly, iron and yeast were given in large doses. If the hemoglobin fell to less than 8 gm. per 100 cc., the drug was discontinued. It was discontinued for other toxic effects when it was believed that more harm than good resulted. Total leukocyte and differential counts and urinalyses were done every two to four weeks, or as indicated. The usual studies for evaluation of the progress of patients at this institution were carried out, i.e., symptomatic response, temperature and pulse measurements, periodic chest roentgenograms, weight determinations, sedimentation times (Linzenmeier), vital capacities, and sputum studies. Other studies were made as indicated. In addition, since Sulphetrone produces anemia and methemoglobinemia with resultant low-grade anoxia, serial electrocardiograms were done in 10 patients.

Clinical Toxicity

Anemia: Table 1 lists the frequency of toxic reactions to Sulphetrone. A fall in hemoglobin was characteristic of all cases during the first three or four weeks of treatment and ranged from 1.6 to 5.8 gm. per 100 cc. Then the concentration varied little until the drug was stopped and within three or four weeks it had returned to its pretreatment value. The average change in hemoglobin for 19 patients who were treated for two weeks or more is shown in figure 1.

Cyanosis: Cyanosis was the next most common toxic manifestation. This was a blue discoloration of the skin and mucous membranes which was probably

TABLE 1

Frequency of Toxic Symptoms due to Sulphetrone in 20 Treated Cases

TOXIC SYMPTOM	FREQUENCY, NUMBER OF INSTANCES IN 20 CASES
Anemia	20
Cyanosis	16
ECG changes	8*
Nervousness	11
Nausea	10
Vomiting	7
Malaise	6
Anorexia	4
Tachycardia	4
Dyspnea	3
Palpitations	2
Blurred vision	2
Headache	2
Hematuria	2
Cystitis	2
Paresthesias	2
Itching	1
Rash	1
Vertigo	1
Somnolence	1
Tinnitus	1
Toxic psychosis	1

* Number of instances in 10 cases.

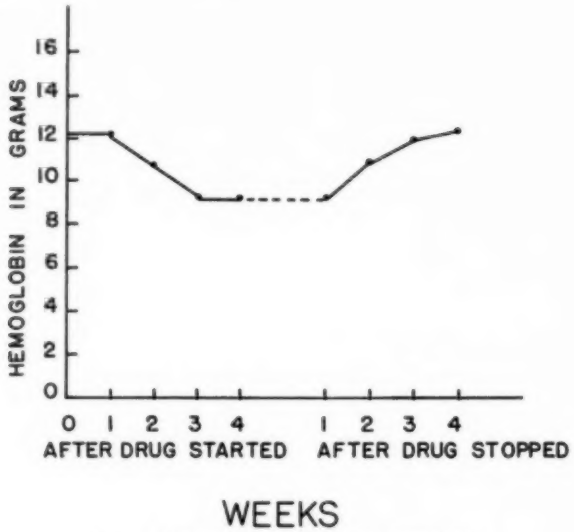

FIG. 1. Effect of Sulphetrone on hemoglobin.

due to methemoglobinemia and, combined with anemia, caused the patient to present a ghastly appearance. The cyanosis was relieved in all 5 patients given methylene blue intravenously in a dosage of 1 to 2 mg. per kg. of body weight. Cyanosis disappeared in fifteen to thirty minutes after the injection and returned in several hours. The degree of cyanosis varied but was present in 80 per cent of the subjects. Moreover, 8 of 10 patients examined showed electrocardiographic changes consistent with the anoxia produced by the drug. Figure 2 illustrates representative T wave changes that occurred in one patient.

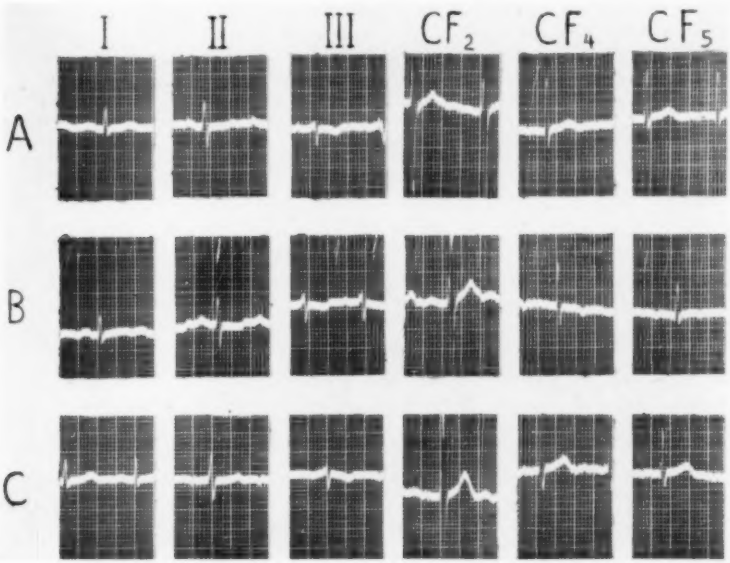

FIG. 2. Illustrative electrocardiographic changes in a patient treated with Sulphetrone. A. Tracing taken before treatment was begun; hemoglobin was 12 gm. per 100 cc. B. Tracing taken three weeks after start of treatment; hemoglobin was 6.6 gm. per 100 cc. and Sulphetrone blood level was 7.0 per 100 cc. C. Tracing taken two weeks after Sulphetrone was stopped; hemoglobin was 8.6 gm. per 100 cc. Note flattening of T waves in leads I and CF_5, and slight inversion of T waves in leads II and CF_4 during treatment with return to normal after treatment was stopped.

Miscellaneous symptoms: Nervousness, nausea, vomiting, and malaise were rather common. Occasionally patients experienced tachycardia, dyspnea, palpitation, blurred vision, headache, paresthesias, itching, rash, vertigo, somnolence, and tinnitus. Hematuria occurred in 2 patients, with symptoms of cystitis in one. One patient had cystitis without hematuria. One patient developed a toxic psychosis after fifteen weeks of treatment. Fortunately, all of these effects were reversible and subsided soon after the drug was discontinued.

Indications for cessation of therapy: Table 2 presents the cases in which Sulphetrone had to be discontinued because of toxic reactions before a full course

of treatment was completed. There was some overlapping in these toxic reactions but, of the 20 patients, only 4 completed fifteen or more weeks of treatment. Anemia and acute toxic reactions accounted for most of the premature

TABLE 2

Toxicity Necessitating Premature Discontinuation of Sulphetrone Therapy

TOXIC SYMPTOM	WEEKS TREATED	NUMBER OF CASES
Acute toxic reaction	0.5 to 4	5
Anemia*	2 to 9	5
Urinary (cystitis, hematuria)	5 to 8	3
Toxic psychosis	16	1
Severe nervousness	6	1
Severe cyanosis and dyspnea	15	1

* Hemoglobin below 8 gm. per 100 cc. of blood

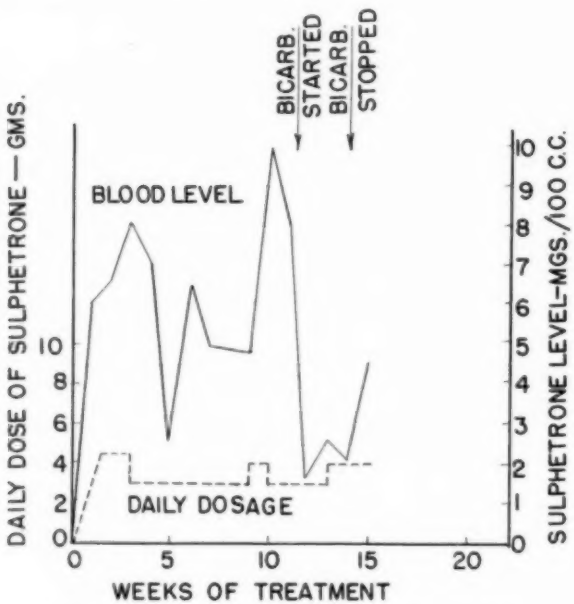

FIG. 3. Influence of dosage on Sulphetrone blood level.

terminations. The acute toxic reaction was related to the Sulphetrone blood level, occurring when the concentration rose to 9 mg. per 100 cc. or more during the first four weeks of therapy. This reaction consisted of nervousness, malaise, nausea, vomiting, tachycardia, palpitation, blurred vision, headache, and some-

times paresthesias and itching. In one patient the blood concentration was 15 mg. per 100 cc. when the toxic reaction occurred. These symptoms all disappeared within forty-eight hours after the drug was withdrawn. In 6 patients, other toxic reactions necessitated discontinuance of the drug. These consisted of urinary symptoms in 3, a toxic psychosis in one, severe nervousness in one, and severe cyanosis with dyspnea in one.

Clinical management of these patients was difficult because it was impossible to predict the concentration of Sulphetrone in the blood which would result from varying the dosage. Several patients developed high blood concentrations on small doses, whereas others were never able to achieve concentrations over

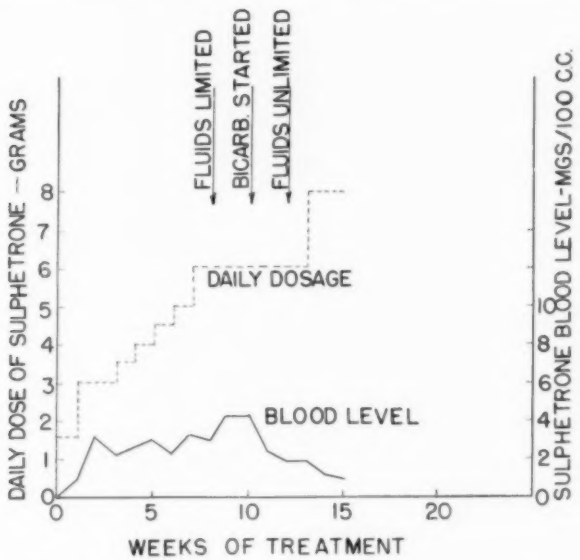

FIG. 4. Influence of dosage on the concentration of Sulphetrone in the blood.

5 mg. per 100 cc. even when the dose was increased to as much as 8 gm. per day and fluid intake was limited to 1,500 cc. per day. The differences in the Sulphetrone blood concentration with variation in dosage are illustrated in figures 3 and 4. Figure 3 shows the response of a patient who attained therapeutic levels rapidly. Variations in dosage caused marked jumps in the blood Sulphetrone concentration. The administration of sodium bicarbonate in doses of 2 gm. per day caused a pronounced drop in the concentration. Figure 4 shows by contrast the response of a patient in whom it was impossible to raise the blood concentration to 5 mg. per 100 cc., even with large doses. Limitation of fluid intake resulted in a small rise in the concentration, but again the administration of bicarbonate caused a precipitous fall, in spite of increased dosage.

COMMENT

Prior to the use of Sulphetrone at this institution, Diasone had been given a trial in 8 patients. These subjects included 5 females and 3 males, who ranged in age from 18 to 50 years. All had far advanced pulmonary tuberculosis. Tuberculous complications included one instance of enteritis, 2 of empyemata, and 2 of pleurocutaneous fistulas. Therapy was carried on for ten days to fourteen weeks. Results were discouraging since only 2 patients showed improvement in their lesions, and these 2 patients had received concurrent streptomycin therapy. The dose of Diasone used was 0.3 gm. three times a day after meals. The hemoglobin concentration fell in all patients from 1.4 to 6.4 gm per 100 cc., in spite of concurrent iron and liver extract treatment and transfusions when indicated. Other complications due to the use of the drug consisted of nervousness and palpitation in one patient and a rash with severe cyanosis in another. This drug was discarded. Our experience with Promin administered orally has been similar, but intravenous Promin is much less toxic and may have a limited usefulness in some conditions such as genitourinary tuberculosis and leprosy.

The management of patients treated with Sulphetrone requires great care. Dosage must be started at a low level and gradually increased as tolerance improves. It is difficult in many patients to obtain a "therapeutic" concentration of drug in the blood of the magnitude that can be established in experimental animals. At the same time it is impossible to predict which patients will attain high concentrations on small dosage and which will never achieve the required concentrations even on high dosage. Therefore, since acute toxic reactions are related to the concentration of the drug, close observation is needed to avoid undesirable reactions. The blood concentration of the drug is influenced by fluid intake in such a way that limitation of fluids causes a rise. On the other hand, the ingestion of sodium bicarbonate causes the blood level to fall.

Anemia was a constant accompaniment of this treatment. Brownlee (4) ascribes this fall in hemoglobin to red-cell hemolysis and to interference with absorption of iron, and perhaps to certain nutritional factors said to be contained in yeast. The concurrent administration of iron and yeast, however, did not prevent a significant fall in hemoglobin which was great enough in many patients to lead to the discontinuance of treatment.

Cyanosis is a very common symptom of Sulphetrone treatment. This seldom gives rise to alarming consequences. However, in one patient it was present to a degree which led us to stop treatment since it was associated with palpitation, tachycardia, and dyspnea. The bluish discoloration of the skin and mucous membranes is, in part, due to methemoglobinemia since methemoglobin is present in the blood to the extent of 4 to 12 per cent. Furthermore, in 5 of our patients, the cyanosis was relieved by the intravenous injection of methylene blue. This is characteristic of methemoglobinemia, for methylene blue is capable of accelerating the normal cell reconversion of methemoglobin to hemoglobin (10). Other unknown pigments may be involved, however, as in sulfanilamide therapy.

The combination of anemia and methemoglobin results in anoxia. Methemoglobin is inert so far as the transportation of oxygen is concerned. It causes a shift of the oxygen dissociation curve to the left and interference with the unloading of oxygen in the tissues (10). Anoxia is therefore the predominant effect of the drug and was shown to exert an influence on the myocardium. Serial electrocardiograms revealed flattening and inversion of T waves in 7 of 10 patients and slight depression of the S-T segment in another patient so studied.

Corper (9) has attributed the antituberculous action of the sulfones to the anoxia produced, since the tubercle bacillus is an aerobe. That Sulphetrone leads to anoxia is apparent from our experience, and Brownlee has reported a lowered oxygen capacity of the blood in patients treated with the drug. But human subjects appear to suffer from this oxygen lack more than do their infecting organisms. The direct antituberculous effect of the sulfones shown in test-tube experiments was not recognized *in vivo*.

The only other serious toxic effects noted in this series were hematuria in 2 patients and a toxic psychosis in one. In addition, symptoms of cystitis necessitated termination of treatment in 2 cases, and nervousness, which was a common manifestation, was severe enough in one patient to warrant cessation of the drug. As a consequence of all of these toxic effects, only 4 of the 20 patients who started treatment were able to take the drug for fifteen weeks, or more.

THERAPEUTIC RESULTS

The results of treatment of pulmonary and mucous membrane tuberculosis with Sulphetrone were disappointing. None of the 5 patients with a recent spread of pulmonary disease showed any change in status during therapy. Of 3 patients with tuberculous enteritis, one showed some symptomatic improvement but in this case the diagnosis was questionable and the patient sensitive to suggestion. Two patients with endobronchial ulceration and granulation exhibited no changes. One of these subsequently responded rapidly to streptomycin but the organisms of the other were streptomycin-resistant.

However, a sacro-iliac lesion with bone destruction and an overlying cold abscess, which had been treated for four months with repeated aspirations and other measures with very little change in status, showed a better response. During three weeks of Sulphetrone therapy, the amount of pus aspirated weekly rapidly lessened, then disappeared.

Hematogenous tuberculids of the feet in one patient disappeared after several weeks of Sulphetrone treatment. Relapse occurred two months after Sulphetrone was discontinued, but healing again resulted when a second course of treatment was administered, again followed by relapse.

General Comment and Summary

Sulfone therapy of tuberculosis has been encouraging in experimental animals, but thus far remains discouraging in humans from the standpoint of both results and toxicity. Sulfones prolong life and diminish the extent of tuberculous infection in guinea pigs with little toxic effects except for splenic enlargement

and cyanosis. On the other hand, the infecting organisms are not killed and the retarding effect disappears when the drug is withdrawn. In humans, the therapeutic effect is slight, and toxicity has been of such a degree as to militate against the use of sulfones except with extreme caution. The present study has confirmed the finding that what is true of previous sulfones is also true of Sulphetrone. In guinea pigs, the combined use of sulfones and streptomycin yields better results than those achieved by streptomycin alone (2). Clinically, such treatment has been tried in a small number of cases (8). Sulfones in low dosage combined with streptomycin may produce better results than streptomycin alone and perhaps delay the emergence of streptomycin-resistant strains of tubercle bacilli. The use of Sulphetrone is fraught with danger unless administration is cautious and subject to careful observation, with frequent checks on the Sulphetrone blood concentration, hemoglobin concentration, and urinalysis. Other less toxic agents with tuberculostatic properties, such as para-aminosalicylic acid, appear more promising as therapeutic agents. The toxic effects of Sulphetrone in the treatment of human tuberculosis appear to outweigh any beneficial effects that result from the use of this drug.

SUMARIO

La Toxicidad Clínica de la Sulfetrona

La sulfonoterapia de la tuberculosis se ha mostrado alentadora en los animales de experimentación, pero hasta ahora continúa siendo desalentadora en los seres humanos, tanto en cuanto a resultados cuanto a toxicidad. Las sulfonas prolongan la vida y amenguan la extensión de la infección tuberculosa en los cobayos, con pocos efectos tóxicos aparte de esplenomegalia y cianosis. En cambio, no destruyen los microbios infectantes y el efecto retardador desaparece al suspenderse la droga. En los seres humanos, el efecto terapéutico es leve, y la toxicidad ha alcanzado tal intensidad que milita contra el empleo de las sulfonas, salvo desplegando suma cautela. Las observaciones de los AA. confirman que lo dicho acerca de las primeras sulfonas reza también con la sulfetrona. En los cobayos, la combinación de sulfonas y estreptomicina da mejores resultados que los logrados por la estreptomicina sola (2). Clínicamente, ese tratamiento ha sido ensayado en un pequeño número de casos (8). Las sulfonas a dosis bajas combinadas con la estreptomicina pueden obtener mejores resultados que la última sola y quizás demorar la aparición de resistencia a la estreptomicina de parte de los bacilos tuberculosos. El uso de la sulfetrona está lleno de peligro a menos que la administración sea cautelosa y objeto de cuidadosa observación, con frecuentes comprobaciones del nivel sanguíneo de sulfetrona, concentración de hemoglobina y y uranálisis. Para el mismo fin, parecen prometer más otros agentes menos tóxicos dotados de propiedades tuberculostáticas, tales como el ácido para-aminosalicílico. En el tratamiento de la tuberculosis humana, los efectos tóxicos de la sulfetrona parecen contrapesar todo resultado beneficioso que pudiera derivarse de su empleo.

Acknowledgment

The authors wish to express their thanks to Harold H. Strauss, Sc.B., for drawing figures 3 and 4.

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VERTICAL TOMOGRAPHY OF THE THORAX[1]

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INTRODUCTION

The present report is concerned with radiography of the thorax, using a vertically moving tomographic system.

There are three reasons for the expectation that upright tomography may be superior to the customary horizontal positioning in investigation of the thoracic contents. (*1*) The first of these is the possibility of projecting the silhouette of a fluid level when free fluid is present in an air pocket. With the subject in the horizontal decubitus, the surface of free fluid lies parallel to the X-ray film and cannot be projected as a linear margin. The demonstration of a fluid surface may be determinative in identifying a radiographic highlight as a pathologic air pocket. (*2*) It is accepted practice that split-second exposures are necessary to exhibit pulmonary detail reliably in radiographs. A modicum of speed of X-ray exposure is easily attained in a vertical tomographic system by the use of gravity, but is mechanically difficult in a horizontally moving unit. (*3*) It is common observation that exposures of the thorax in the prone and supine positions do not well duplicate or as clearly delineate pulmonary lesions as do upright exposures of the same subject. This is presumably due to altered distribution of the thoracic wall tissues by pressure and gravity; and to altered form of expansion of the lungs by interference with freedom of movement of the diaphragm in these positions. Upright tomography may then be expected to be biased towards duplication of the plain film silhouettes.

EXPERIMENTAL OBSERVATIONS

A series of 904 separate lungs were radiographed with a vertically moving tomographic system, and the silhouettes compared with those in the plain upright films of the same subjects. The studies were chiefly concerned with problems in pulmonary tuberculosis, and the most important single issue was the identification of tuberculous cavity.

Minimal technical requirements were found to be an exposure time of not more than one-quarter of a second; moving Bucky grid; and 1.5 mm. focal spot at 36-inch target-film distance. A normal range of contrast, density, and sharpness of image was attained with these constants, comparable to the standards customary for plain radiographs. "Layers" were exposed at 1, 1.5, or 2 cm. intervals, varying with the problem involved.

The indications for layer radiography of pulmonary lesions are of course basically the same as for other parts of the body, namely, to separate superimposed silhouettes by "smearing" and homogenizing the shadows of the undesired parts.

The structures which most commonly eclipse and obscure the shadows of pul-

[1] From the Beck Memorial Sanatorium, London, Ontario.

monary lesions are: (a) the normal thoracic bones (The single most important point of hazard is the overlying position of the clavicle and one or more ribs.); (b) regenerated bone following thoracoplastic surgery (This commonly produces eclipsing shadows of high density, and may produce artificial rings which are specifically confusing in terms of underlying cavity.); (c) multiple pulmonary lesions (The denser portions of lesions may overlie and interfere with visibility of lighter portions.); (d) the mediastinal organs which form a composite shadow of multiple dense components. The domes of the diaphragm may also eclipse significant pulmonary opacities.

Demonstration of cavities: Tables 1 and 2 are tabulations of the frequency with which cavities and fluid levels were interpreted in vertically exposed tomographs of different pulmonary problems. The essence of table 1 is the identification of the probable presence of one or more cavities in 44 per cent of the lungs examined with this technique. In the plain radiographs of the same subjects, cavities were not identifiable in about 70 per cent of the series, and were suspected but not clearly demonstrated in the remaining 30 per cent. The majority, but not all, of the patients exhibited tubercle bacilli in the sputum.

TABLE 1

904 Lungs Examined by Vertical Tomography

	NUMBER OF CASES	PER CENT OF TOTAL
Total cases with cavity interpreted by tomography	398	44
Cases with fluid level interpreted in cavity by tomography	190	21

Approximately 300 of these lungs were collapsed by surgical means, with visibility usually severely impaired by overlying regenerated bone. The remainder (about 600 lungs) were problems in relatively light-density, disseminated, tuberculous lesions in which the existence of cavity was indeterminate. No gross difference in the proportion of cavities shown is demonstrated for these different classes of problems. However contrary to expectation, the method proved to be as valuable for cavity diagnosis in untreated lung lesions as in postsurgical problems.

Fluid levels in cavities: Table 1 further shows that the coexistence of free fluid was interpreted in about one-half of the cavities identified, though not visible in the corresponding plain films. A fluid level may be taken to be a near approach to certainty in the identification of an air pocket. Approximately one-half of these fluid lines were self-evident fluid "puddles" such as are frequently seen in large pulmonary cavities in plain radiographs. The remainder of the shadows interpreted as fluid levels were more tenuous silhouettes.

The criteria used for classifying "line-shadows" in vertical tomographs as probable fluid levels were: (a) knife-edge sharpness and straightness, (b) strictly horizontal direction, (c) beginning and ending strictly at the margins of the suspect cavity. The supreme test is of course to demonstrate that the line re-

mains horizontal when the patient is tilted to one side. Although this has been done in selected cases, the demonstrations as recorded are not based upon this test.

Although frank fluid puddles are visible in only a proportion of cavities, since these are basically exuding surfaces, it may be assumed that the floors of the majority are "wet." It is then not surprising that the layer-selectivity of vertical

TABLE 2

Types of Tuberculous Problems Explored by Vertical Tomography

	NUMBER OF CASES	PER CENT WITH CAVITY INTERPRETED
Postthoracoplasty problems	245	40
Therapeutic pneumothorax	56	39
Parenchymatous infiltrations	603	53
	904	average 44

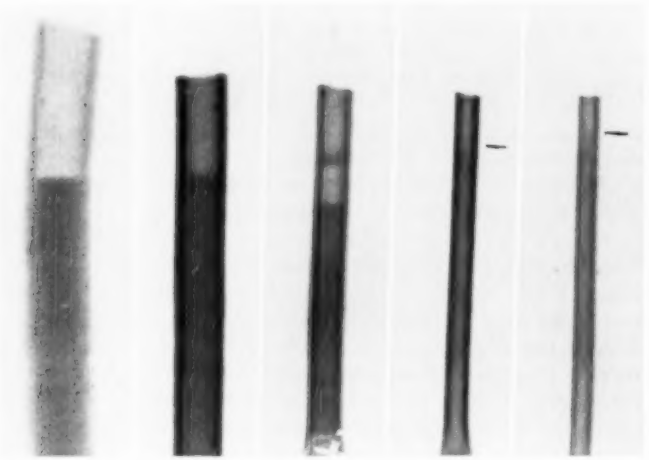

FIG. 1. Vertical tomograph of same region showing cavity with fluid level.

tomography should materially increase the proportion of fluid lines that become visible.

Experimental fluid levels: The size of cavity in which free fluid may be identified radiographically has been studied experimentally. Figure 1 is a reproduction of a tomographic exposure of rubber tubes containing water, placed 12 cm. from the film (corresponding to the back of the thorax) and eclipsed by a two-inch block of paraffin to duplicate the density of the muscles of the thorax. It is seen that the fluid level is easily identified under these conditions in tubes as narrow

as 3 mm. in bore and may be discerned faintly in tubes of 2 and 1 mm. bore. It is seen also that in 0.5 cm. or larger tubes the fluid line is "straight" but that in smaller bores the margins curve upwards due to capillary attraction. This effect is often visible in radiographs of actual cavities and should be recognized as part of the evidence in interpreting film shadows.

The observer may also consider whether a mere smoothing of the silhouette of the floor of a cavity, even when not "straight" horizontally placed, or "flowable," may not reflect a surfacing effect by a capillary layer of fluid, and provide legitimate suspicion towards the interpretation of cavity.

Criteria for the recognition of cavity: When no fluid level is demonstrable, the criteria for interpretation of cavities in tomographic silhouettes are basically the same as for plain radiographs. These are a "highlight" with a complete wall in relationship to a parenchymatous lesion.

The tomographic silhouettes supply additional data, however, to those inherent in the plain film shadows as follows:

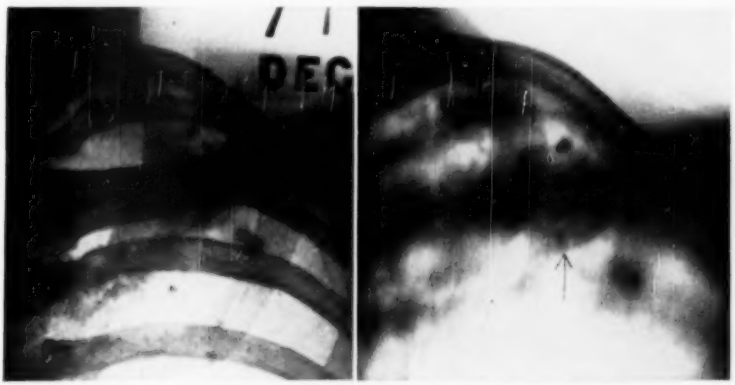

FIG. 2. (Left) Plain film. (Right) Vertical tomograph of same region showing cavity with fluid level.

(a) Increased visibility of image due to the tomographic principle of obliterating otherwise superimposed shadows. This effect is sometimes dramatic in degree (see figures 2 and 3) and cavities often become apparent at unexpected positions. We have been unable to find that this visibility can be duplicated by other special regional techniques such as altered penetration and angle of exposure.

(b) Demonstratation of whether or not a ring shadow is coexistent with lesion in the third dimension of depth.

(c) Demonstration of whether a ring shadow is complete at one plane, or is a composite shadow derived from eclipsing images at different depths.

(d) The same principles may result in projection of a smaller ring shadow in the films exposed at adjacent levels to the optimum focus. Progressive increase and decrease in the diameter of a ring shadow in serial tomographic layers is rather convincing evidence of "slicing of a sphere."

Cavities which are demonstrated by tomography exhibit the same range of shapes as are regularly observed in plain films, namely, oval, egg-shaped, spherical, and dome- or "chocolate-drop"-shaped with a flattened bottom. A flattened floor in a cavity may well be conditioned by a state of chronic or recurring fluid exudate predisposing to erosion at this position. Even in the absence of visible free fluid a flattened distal contour in a ring shadow may be predisposing evidence towards interpretation of cavity.

Nonspheroidal cavities: Tomographic films show frequent additional amorphous-shaped "highlights," however, which conform to the criteria of cavity formation. These may be flattened, triangular, or lobulated, et cetera, and may exhibit coarsely crenated or toothed margins, in contrast to the usually smooth outlines of plain film silhouettes.

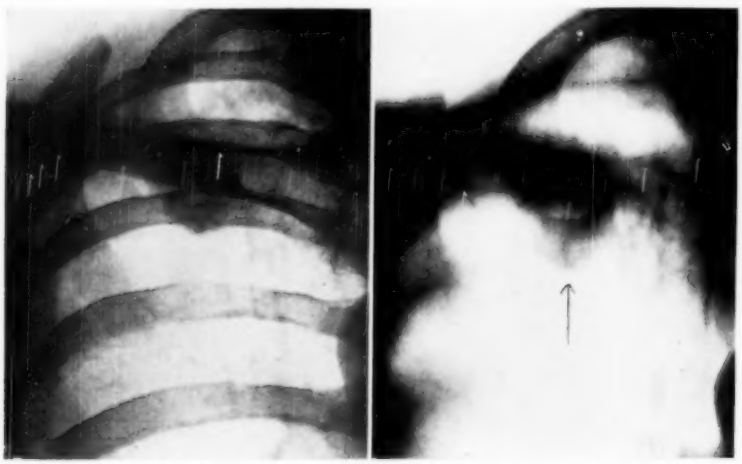

FIG. 3. (Left) Plain film. (Right) Vertical tomograph of same region showing cavity with fluid level.

There is probably a sound pathologic basis for these variants in tomographic cavity outlines. Moolten in 1935 (1) and the present writer in 1938 (2) showed that a mechanical interruption of lung tissue, i.e., a simple tear, can result in characteristic cavity formation, and that it is not necessary to postulate excavation (the removal of a corresponding volume of dead tissue) to explain tuberculous cavities. These observations are applicable to the common smoothly outlined spheroidal or balloon cavities. In sectioning tuberculous lungs removed at autopsy, however, it is common to encounter many small amorphous-shaped cavities in caseous tissue, in addition to the larger spheroids evident in the radiographs. It may be considered as probable that tomography can bring into range of visibility cavities which are in reality *excavations* in caseous tissue, in contrast to the common balloons which are probably smoothly dilated tears.

SUMMARY AND CONCLUSIONS

Radiography of the lungs by vertical speed tomography[2] materially increases the frequency and certainty of tuberculous cavity identification. Since the management of pulmonary tuberculosis is in essence the management of cavities, the method constitutes a highly significant advance in phthisiologic practice.

SUMARIO Y CONCLUSIONES

Tomografía Vertical del Tórax

La radiografía de los pulmones con la tomografía rápida vertical acrecienta decididamente la frecuencia y certeza con que se identifican las cavernas pulmonares. Como la asistencia de la tuberculosis pulmonar viene a ser en el fondo asistencia de las cavernas, dicha técnica parece constituir un adelanto importante en la práctica tisiológica.

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[2] Principles by which amateur construction of a vertical tomograph is possible with available materials are in press in "The Focal Spot," Journal of the Canadian Society of Radiological Technicians (Toronto). A Canadian manufacturer is offering a self-contained X-ray vertical tomographic unit incorporating the principles followed in this study.

EXPERIENCES WITH SURGICAL RECONSTRUCTION OF THE TRACHEA[1]

PAUL W. GEBAUER

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INTRODUCTION

Wire-enforced dermal grafts have been singularly successful in the surgical correction of severe bronchostenosis resulting from healed tuberculosis (1, 2). Generally, pulmonary resection is required for this disorder because the segment, lobe, or lung distal to the stenosis is thoroughly diseased. Nevertheless, in a small group of patients, the bronchus heals and the lung remains clear or also heals, whereas symptoms resulting from the bronchial stricture persist. In a somewhat larger group of patients, the parenchymal disease is confined to one lobe, while a stenotic process involves the main bronchus, thus functionally impairing and eventually destroying the remaining lobe or lobes. In such instances, removal of the diseased lobe and preservation of the remaining lobes by a dermal graft of the main bronchial stenosis is more logical treatment than resection of everything distal to the stenosis. Thus in the writer's series pneumonectomy has been avoided in 8 patients, resulting in a total salvage of eleven separate lobes which would have been sacrificed by pneumonectomy. In another patient, no pulmonary resection was necessary, and symptoms were relieved by a dermal graft of a main bronchial stenosis. A second similar case is reported in this paper.

Because dermal grafting has been so successful for the relief of bronchial stricture, and also successful in one instance of tracheal stricture, it is believed that its use in the treatment of tracheal deformities might become common, at least until a better method is disclosed. Because the surgical treatment of tracheal obstruction and deformities differs considerably from the treatment of bronchial defects, it is believed that the relation of the writer's experiences might prevent a repetition of certain mistakes by other surgeons. For this reason, 4 cases of severe tracheal stenoses treated surgically are reported, despite the fact that a 75 per cent case mortality rate does not ordinarily lend itself to the publication of an operative procedure.

The clinical and experimental background for the use of dermal bronchial grafts has been elaborated (1), and the operative technique described (2). The method employed for bronchial strictures is diagrammatically presented in figure 1, and has been described in detail (1, 2). Briefly, the stenotic bronchus is incised along its posterior surface, the incision spread open, and the resulting defect filled with an inlay graft of dermal skin obtained from the primary thoracotomy incision. The patch of dermal skin is fashioned to fit properly into the bronchial defect. Before it is sutured in place with No. 35 atraumatic, multistrand, wire sutures, the dermal skin is provided with a desirable semi-rigidity by lacing

[1] From the Thoracic Surgical Service of Leahi Hospital, Honolulu, Hawaii.

through its substance, from side to side, a strand of No. 30 stainless steel wire. This provides an embedded rib-like support for the graft and permits it to be

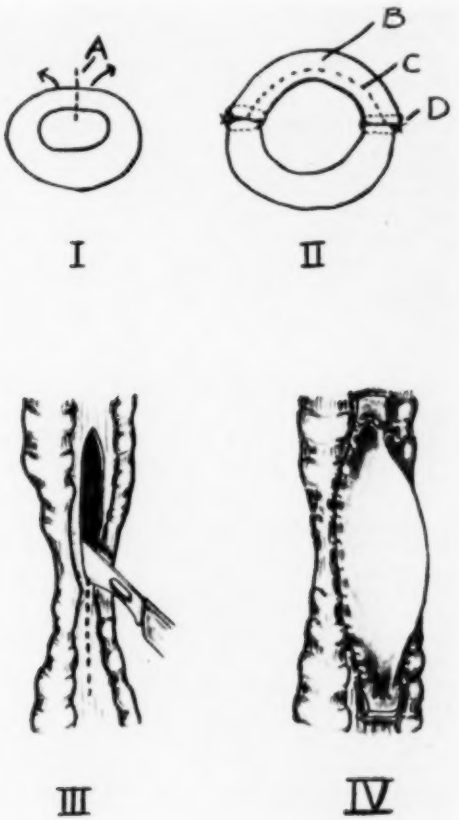

FIG. 1. Drawings illustrating the principle and technique employed in dermal grafts of the bronchi. I. Cross section of a stenotic bronchus. Dotted line A indicates incision of posterior membranous wall. II. Stenosed bronchus has been spread open, and posterior half now consists of a rounded graft of dermal skin(B), with embedded wire structure (C) forming a supportive framework. D indicates wire sutures which hold the graft to the bronchus and also include the loops of the wire framework along the edges of the graft. III. Posterior aspect of a stenotic bronchus being incised. IV. Bronchus opened and defect filled with an inlay dermal graft. The embedded wire forming the skeletal framework is not shown; it is a continuous wire running from side to side.

molded into a rounded contour, thus furnishing a round lumen rather than a slit lumen for the grafted bronchus.

CASE REPORTS

Case 1: M. R., a 44-year-old female with known bilateral apical tuberculosis for four years, was bronchoscoped in April 1948 because of threatening asphyxia. Her sputum was occasionally positive for tubercle bacilli. Paroxysms of cough and wheezing had been increasing in severity. A healed stricture, forming an unbelievably small lumen, was encountered in the upper trachea. Immediate tracheotomy revealed a severely scarred trachea. A small, granular, tortuous lumen was located with difficulty. Within a week tracheotomy had to be repeated because of obstruction distal to the tube. A month later obstruction recurred distal to the longer second tube, and the patient was transferred to Leahi Hospital.

On June 6, 1948, the day of admission, she was dyspneic, cyanotic, and emaciated, with a temperature of 102° F. and a pulse of 160 per minute. It was apparent that she just existed from one tube cleansing and tracheal aspiration to the next. With oxygen insufflation, laryngoscopy and tracheoscopy were carried out. Tissue removed from the lower trachea showed a nonspecific, fibroplastic inflammation of thick stratified, squamous epithelium. A long No. 6, "cane"-type tracheotomy tube was inserted with considerable difficulty. Roentgenograms of the chest showed scattered fibrotic and productive lesions of both apices, more marked on the right, and possible emphysema of the right lung.

Penicillin, streptomycin, sulfadiazine, and daily intravenous fluids, including blood, plasma, and amino acids, were administered. A day and night regimen of steam and oxygen inhalations, repeated tracheal aspirations, and oral cleansings was instituted. In ten days her general condition improved considerably and she indicated that she felt better. However, the slightest amount of secretion in the terminal trachea produced cyanosis and dyspnea. Planigrams revealed no lung cavities, a normal left main bronchial shadow, but no demonstrable lumen in the trachea or the proximal right main bronchus.

Operation: Because of the obviously hopeless prognosis and her highly precarious existence for the previous two months, it was decided to attempt excision of the chronically inflamed, stenotic trachea, and to substitute a tube of fascia lata wrapped around a coil of stainless steel wire (figure 2, I). A similar procedure had been briefly described by Belsey (3). The plan of the operation is diagrammatically presented in figure 2, II and III. The plan was to excise the trachea, pass the fascial tube over the tracheal catheter, and insert the latter into the left main bronchus. The inferior end of the fascial tube was to be sutured to the tracheal bifurcation. The upper end of the fascial tube was to be exteriorized in the lower neck through a second approach, or possibly sutured to the subglottic trachea.

Spiral coils of varied diameters made from stainless steel wire of No. 28, No. 30, and No. 32 gauges were prepared beforehand, and operation was undertaken June 16, 1948. Figure 2, II depicts the tracheobronchial deformity present. After topical anesthesia, a No. 29 tracheal catheter was forced through the tracheotomy opening and into the left bronchus. A satisfactory air exchange resulted. General anesthesia was induced with cyclopropane-ether and controlled positive-negative pressure. The tracheal catheter was fixed to the skin of the neck with a suture. While a second team obtained fascia lata from the thigh, the trachea was exposed through a right posterior thoracotomy; it was represented by a thick, fibrotic tube, tightly stretched over the tracheal catheter, and was recognized only by some remnants of cartilage rings in the left lateral wall. As the tracheal catheter passed the carina, it completely occluded a severe stenosis of the right main bronchus, and the right lung was blocked in a distended state. Therefore, it was necessary for the anesthetist to remove the skin suture and draw the tracheal catheter upward. After this, adequate exposure was obtained by manual compression of the right lung. The trachea was dissected free from the lower neck to the bifurcation. By this time, the second operative team had constructed a fascial tube over a selected coil of wire, and it was ready for substitution of the trachea. A finger was passed under the tracheal bifurcation, preparatory to its division. The tracheal catheter was not felt, and the previously strong aortic pulsations were absent. The clicking, "on and off," of the controlled breathing apparatus continued, but the tracheal catheter had slipped completely out of the trachea and was found outside the cervical tracheostomy.

The patient had asphyxiated in the short period her respiration had not been supplied. The trachea was opened, and attempts at resuscitation were abandoned after ten minutes.

Post-mortem examination: Post-mortem examination of the trachea disclosed a narrow granular lumen extending from the carina upwards to the previous location of the tracheotomy tube, where the lining was smooth and the lumen larger. Above the tracheostomy in the neck and extending to the subglottis, the trachea was filled with friable granulation tissue. The stenosis of the right main bronchus was very short and present only at the carina. It could have been opened and covered by the fascial tube.

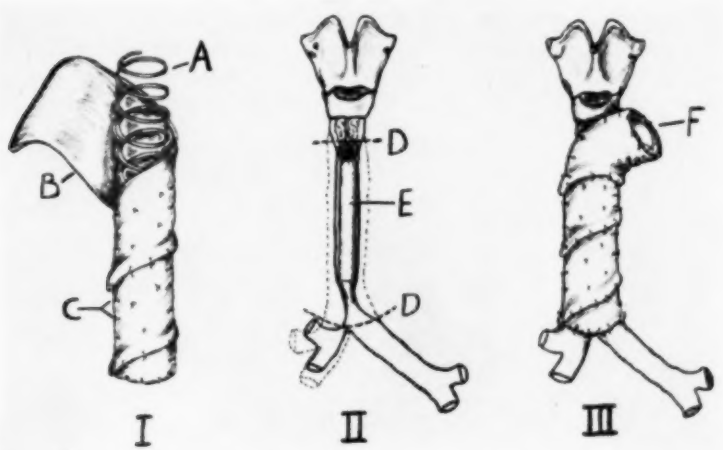

FIG. 2. Case 1. (M. R.) Drawings illustrating the construction of an artificial trachea and proposed plan of operative treatment. I. A. Coil of stainless wire. B. Fascia lata wrapped in a spiral about the coil, and fixed to it with fine wire sutures (C). II. Diagrammatic representation of the status of Case 1. D. Proposed lines of tracheal excision. E. Former location of tracheotomy tube with tracheostomy at the upper end. Note granulation tissue between larynx and tracheostomy, and between bifurcation and distal end of tracheotomy tube. III. Diagram depicting the proposed replacement of the trachea. F. Upper end to be exteriorized through a second approach in the neck.

Comment: The appearance of the upper trachea indicated that it would have been advisable to exteriorize the fascial tube in the neck, rather than attempt a connection with the subglottis. This also would have simplified the postoperative care. However, it is almost certain that infection would ultimately accompany such a tracheotomy, and thereby the possibility of eventual healing, or of a natural regenerative replacement of the fascial tube, would be hindered. This possibility may exist, but it is believed that the procedure herein described, even under the most favorable conditions, would ultimately fail. Complete excision of all the tracheal structures, even if they are merely remnants, leaves no opportunity for regeneration, and the possibility of survival of such a large area of fascia with one surface exposed to the air passages, especially in the presence of a foreign body (wire coil), is highly unlikely. Certainly an adequate,

air-tight passage could be provided for a time, but once fascial slough began it is reasonable to assume that even greater difficulties than those originally posed by this patient would have occurred.

A few moments of relaxed vigilance in regard to oxygenation and respiratory exchange in a debilitated patient with an airway on the borderline of adequacy may produce fatal myocardial asphyxia. This possibility is especially great during positive-negative controlled respiration, when the breathing lung is not in view. As a rule, the respiratory movements of the patient are hardly perceptible or are masked by operative traction and manipulation. One tends to form the habit of appraising the patient's respiration by the sounds or functioning of the breathing apparatus. In the opinion of the writer, the fundamental cause of death in this patient was a false sense of security in controlled breathing.

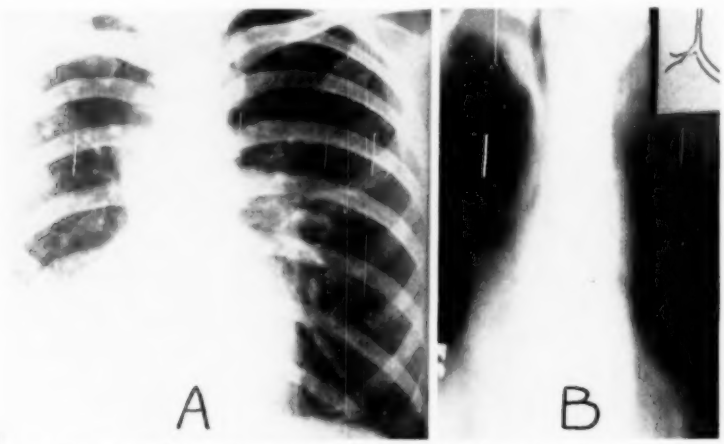

FIG. 3. Case 2. (C. M.) A. Preoperative chest film showing atelectasis of the lower and middle lobes and tuberculous infiltration in the upper lobe. The left lung is clear. B. Planigram showing severe stenosis of the lower trachea and the right main bronchus.

Case 2: C. M., a 26-year-old female, was hospitalized for four years. During the latter half of this period, a severe ulcerocaseous tuberculous tracheobronchitis was observed bronchoscopically. The process involved the right main bronchus and the lower two-thirds of the trachea. It was always most marked anterior and along the right lateral tracheal wall. It was accompanied by a gradual, progressive tuberculosis of the right lung. Three months' treatment with streptomycin produced healing of the tracheobronchitis, but progressive stenosis of the lower trachea and right intermediate bronchus followed. Atelectasis of the right lower and middle lobe occurred. The lower half of the trachea became severely stenosed. The irregular lumen just above the carina was approximately 4 by 2 mm. and precluded examination distal to this point. The right intermediate bronchus was functionally occluded. The state of its healing could not be determined. The aerating right upper lobe contained extensive, rather stable infiltration. Figure 3 illustrates the involvement of the right lung; the planigram indicates the severe tracheal and bronchial stenoses. The sputum was positive for tubercle bacilli; there was a low-grade, intermittent fever, and the pulse

varied between 90 and 100 per minute. At times cyanosis was definite, and a marked wheeze was audible at the bedside. On serial bronchoscopic examinations it could be seen that the tracheal stenosis was increasing and the patient was failing clinically. Tubercle bacilli cultured from the sputum were sensitive to streptomycin, and there was no clinical involvment of the left lung. Right pneumonectomy was desirable but contraindicated by the severe tracheal stenosis. It was decided that excision of the right lung after reconstruction of the tracheal stenosis with a dermal graft offered the patient the only chance of recovery.

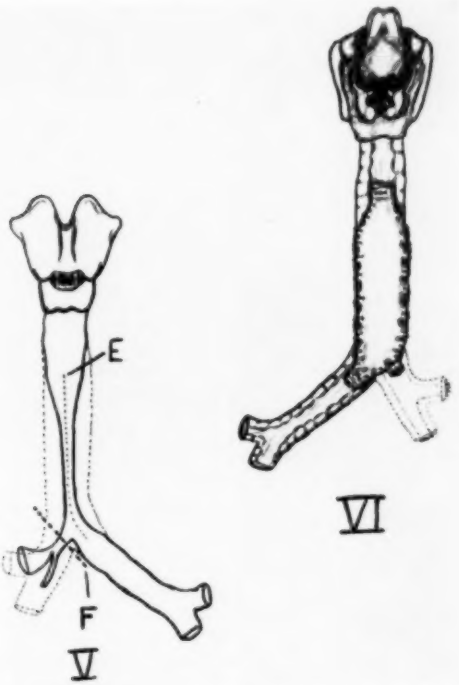

FIG. 4. Case 2. (C. M.) V. Diagram representing tracheobronchial deformity of Case 2 from anterior aspect. E. Proposed line of incision along posterior tracheal wall. F. Line of excision of right lung. VI. Proposed operative treatment of Case 2, from posterior aspect. The right lung has been resected; the tracheal graft extends over the bifurcation.

Operation: The operative plan is depicted in figure 4, V and VI. On October 20, 1948, a tracheal catheter was inserted down to the stenosis. Cyclopropane-ether anesthesia was obtained with difficulty. A right posterior thoracotomy was carried out to expose the posterior tracheal wall in order to incise it and draw down the tracheal catheter for insertion into the left main bronchus. Evidently the tracheal stenosis was too severe to permit an adequate gaseous exchange under the stresses of a major surgical procedure, although it had allowed fairly comfortable breathing with the patient lying in bed. The pulse rate and respirations gradually climbed; a satisfactory color could not be persistently maintained, even with controlled respiration. Exposure of the tracheal bifurcation was readily accomp-

lished, but there was difficulty in freeing the upper portion of the stenosis. Before it could be incised, circulatory collapse occurred. The bifurcation was opened and an airway obtained, too late, however, to allow successful resuscitation. Under such circumstances there is no time for improvisation. If immediate entry to the left bronchus had been gained, and a means of supplying respiration to it had been available, it is considered to be virtually certain this patient would not have expired.

Comment: Before undertaking surgery for tracheal obstruction, whether or not a tracheotomy is present, a means of applying controlled breathing through the chest wound should be at hand. From the lower trachea either main bronchus can be intubated and connected to sterile anesthetic tubing in order to by-pass any airway obstruction above the bifurcation. For the next patient herein reported, such a sterile setup was prepared. It consisted of various-sized tracheal catheters and connections, plus sterile tubing for the anesthesia apparatus.

Case 3: M. T., a 34-year-old male, has been previously reported in detail (2). Briefly, he had been known to have had tuberculosis for 14 years and the lesions in both lungs were healed (figure 5, A). The sputum had been negative for tubercle bacilli for two years. He had a severe wheeze, productive cough, six to eight ounces of frothy mucoid sputum per day, and periodic dyspnea. He was willing to undergo anything for relief. Bronchoscopy and planigrams (figure 5, B and C) disclosed a severe stenosis of the distal trachea, and the right intermediate and lower lobe bronchi.

Operation: On March 2, 1949, right posterior thoracotomy was performed, the tracheal stenosis incised, and the contained catheter drawn down and inserted into the left main bronchus. It was not necessary to provide an airway through the wound. The tracheal defect was repaired with a dermal graft, inserted and sutured in place over the tracheal catheter. A second dermal graft was then used to reconstruct the right main bronchus (figure 6, I and II). A large cluster of subpleural blebs was excised from the apex of the upper lobe.

The patient made an uneventful recovery. The right lung expanded readily; wheeze and dyspnea disappeared. Some cough and sputum amounting to three to four ounces per day continued. Roentgenograms showed aeration of the posterior basal segment of the lower lobe which had previously been atelectatic. Bronchoscopy revealed early healing of the grafts and an excellent tracheal lumen has persisted. The right main bronchus is about one-half normal size and the accumulation of mucus within it periodically produces audible coarse rhonchi.

Three months after operation, a cyst appeared in the apex of the upper lobe. It enlarged. One month later it was closed by a short period of transthoracic catheter suction. It has remained closed for seven months (figure 7, A, B, C). The patient's respiratory function tests are excellent, his tracheal lumen is practically normal (figure 7, D and E). His symptoms are more than 50 per cent improved. Possibly a revised reconstruction of the right bronchus, and right lower lobectomy for residual bronchiectasis, or further cystic formations will be advisable in the near future. The sputum is negative for tubercle bacilli.

Comment: This case definitely demonstrates the feasibility of tracheal reconstruction with dermal grafts. The tracheal result is all one could hope for. The bronchial graft is not quite satisfactory. In all probability, the patient's symptoms are aggravated by cystic and emphysematous changes in the right lung. These were discovered first at operation and evidently are still progressing. Perhaps this progression is accentuated by the diminished right bronchial lumen; on the other hand, it could be secondary to healed pulmonary scars and not

related to the bronchial lumen. Unquestionably, the experiences of the preceding two cases, and the previous bronchial grafts, contributed significantly to the favorable outcome.

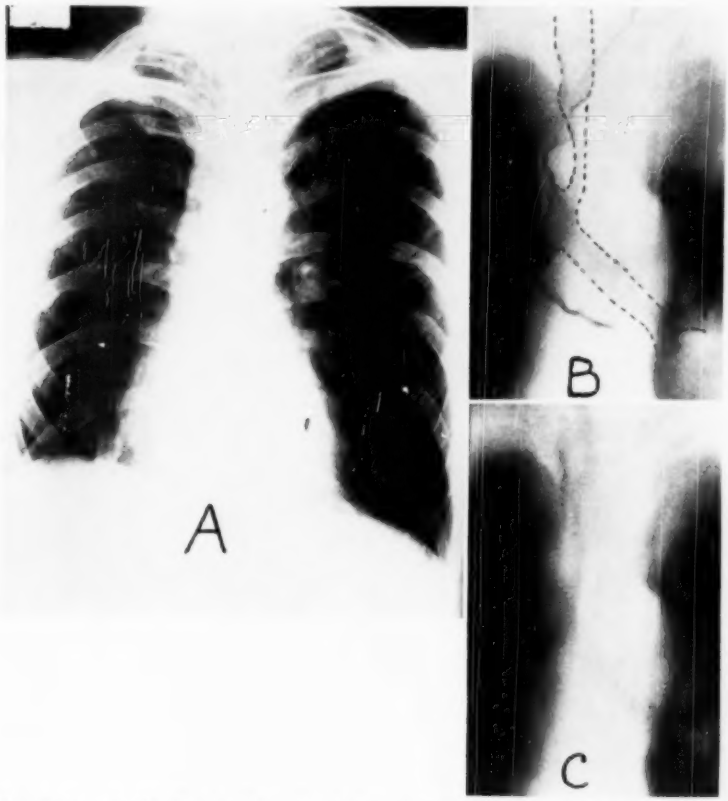

FIG. 5. Case 3. (M. T.) A. Chest film before operation shows scarring in the extreme apices and basal segment atelectasis along the right cardiac border. B. and C. Marked and unmarked planigrams of the trachea and bronchi before operation (compare with figure 6, I). There is severe stenosis of the lower trachea and distal right bronchus.

Case 4: M. I., a 26-year-old female, had minimal pulmonary tuberculosis of the right upper lobe with bronchial symptoms. Over a 14-month period, a severe ulcerocaseous tuberculosis, involving the proximal right main bronchus and distal half of the trachea, was observed bronchoscopically. Stenosis accompanied the healing process which followed symptomatic treatment and streptomycin. After 11 months, the usual symptoms of tracheobronchial obstruction increased in severity; the tracheal lumen decreased, and the right upper lobe infiltration spread slightly. A low-grade fever persisted. The sputum again became positive for tubercle bacilli. The trachea appeared healed, but it was impossible to pass a

5 mm. bronchoscope beyond the stenosis. It was decided to graft the tracheal stenosis, to extend the graft beyond the stenosis of the proximal right bronchus, and to excise the right upper lobe. However, reontgenograms obtained the day before operation showed increasing atelectasis as illustrated in figure 8, A, B, C, and D. Because of the atelectasis and possible spread of her disease, the extent of resection was to be determined by the operative findings. Cultures of tubercle bacilli isolated from the patient's sputum were still sensitive to streptomycin.

Operation: Operation was performed on October 19, 1949. A 32F tracheal catheter was passed through the larynx, and a right posterior thoracotomy performed. The tracheal

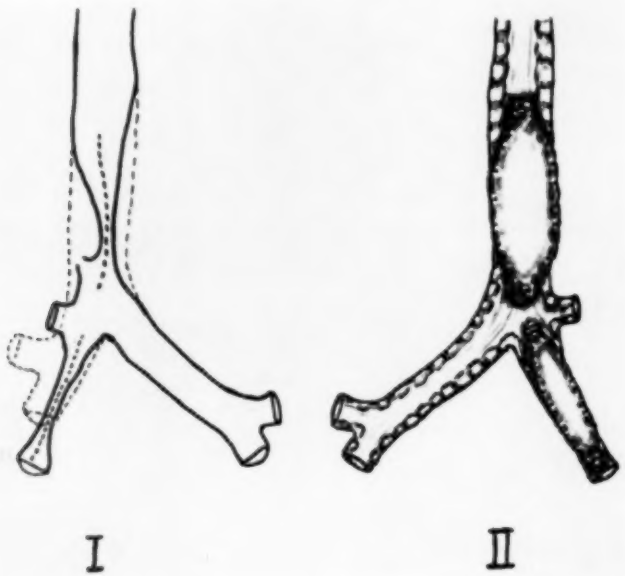

FIG. 6. Case 3. (M. T.) Drawings presenting the operative procedure used in Case 3. I. Anterior view diagrams of deformities encountered. The dotted lines indicate the incisions of the posterior membranous surfaces of the trachea and right bronchus. II. Posterior view diagram showing the two dermal grafts inserted.

stenosis was incised. The tracheal catheter distended the upper trachea above the stenosis, and it was drawn down with considerable difficulty. It was inserted into the left main bronchus. The right middle and lower lobes were completely atelectatic, as was the lateral or axillary segment of the upper lobe, in which nodular infiltration was palpable. The posterior wall of the right bronchus was incised; a severe, short, healed stenosis existed at the carina. Incision released a copious flow of thick, tenacious, slightly cloudy mucus; more of the same was aspirated from the lobar bronchi. Because of the recent changes in the roentgenograms, and the "positive" sputum, it was considered that a tuberculous spread possibly existed in the lower and middle lobes which was not palpable or grossly detectable. If such were the case, healing of a tracheal graft would certainly be jeopardized. Therefore a right pneumonectomy, rather than upper lobectomy, was done, and the trachea grafted as de-

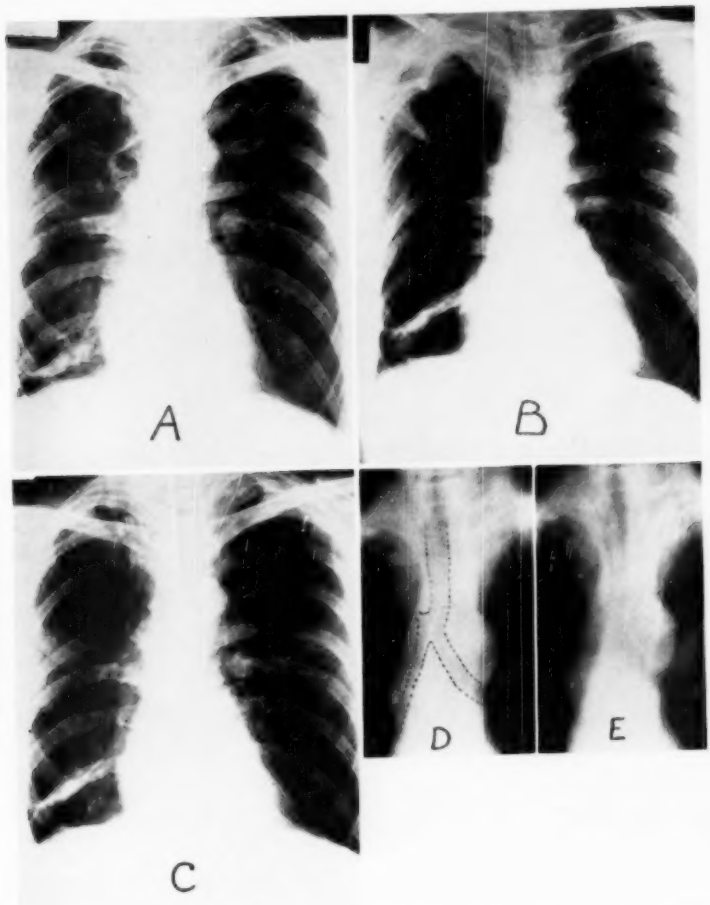

FIG. 7. Case 3. (M. T.) Postoperative chest roentgenograms. A. Three months after operation, a large cyst is present in the right upper lobe. A large cluster of subpleural cysts had been removed from the extreme apex of the upper lobe at operation. B. The cyst is collapsed by suction through the transthoracic catheter in the right apex. C. Eight months after removal of the catheter and eleven months after operation, the cyst is still closed. Possibly another cyst in the lateral portion of the right base is appearing. The preoperative atelectasis along the right cardiac border has cleared, and the density overlapping the central right diaphragm (compare with figure 5, A) has shifted upward and to the right. D. and E. Marked and unmarked planigrams of the trachea and bronchi eleven months after operation.

picted in figure 9. Just before completion of the graft sutures, the anesthetist pulled the tracheal catheter up, drawing it out of the left bronchus into the upper trachea. This was

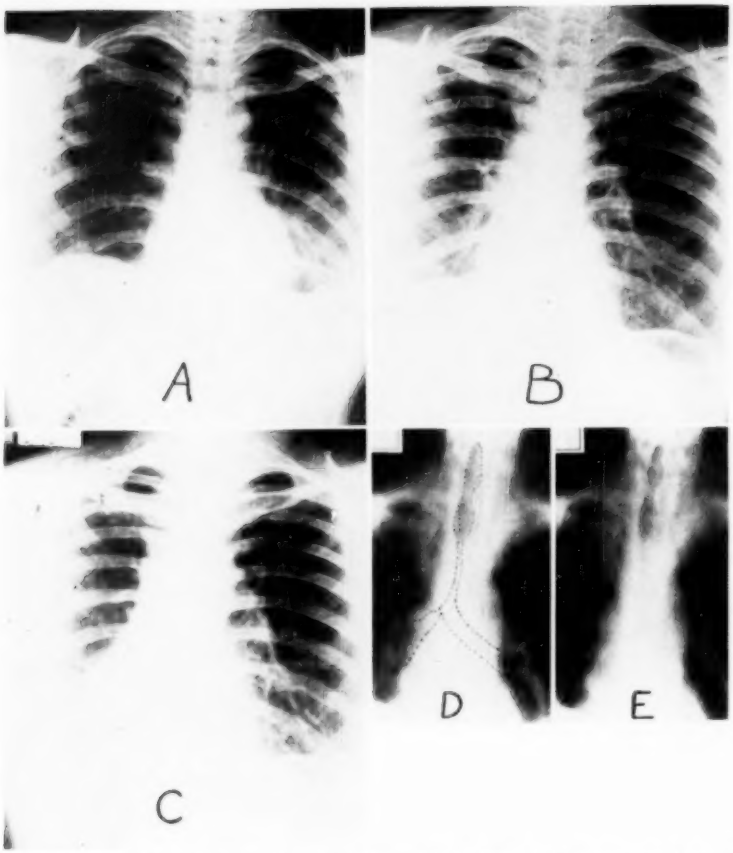

FIG. 8. Case 4. (M. I.) Preoperative chest films and planigrams. A. Expiratory chest film showing block of the right lung in a partially distended state. B. Inspiratory film, descent of the left diaphragm, poor aeration of the right base, and light infiltration in the right upper lobe. A and B were taken six days before operation. C. Inspiratory film taken the day before surgery now shows atelectasis of the right middle and lower lobes. Because of this change the extent of pulmonary resection was considered dependent on the operative findings. D. and E. Marked and unmarked planigrams of the trachea and bronchi before operation showing severe stenosis of the lower trachea and proximal right bronchus. There is also some narrowing of the upper trachea. Compare with figure 9, I.

extremely difficult because the catheter seemed "glued" to the upper trachea above the graft. It was finally accomplished by a hard, continuous tug. The operation was completed without difficulty.

Postoperatively the patient did well, except for rasping tracheal breath sounds. On the second day a wheeze and moderate dyspnea developed. Bronchoscopy revealed partial obstruction of the upper trachea by edema and sloughing sheets of thin mucosa, which were

removed by suction. The grafted portion of the trachea and the right bronchial stump looked good, and the lumen easily admitted a standard 7 mm. bronchoscope into the left bronchus. The picture was thereafter much improved until the third postoperative morning, when an incredible quantity of detached mucosa was again aspirated from the upper trachea. In addition, the tracheal wall anterior to the graft was edematous, as was the orifice of the left main bronchus. The patient was again improved, but the pulse, respiration, and temperature began to climb. It became obvious that the respiratory capacity of the left lung was inadequate in the presence of a narrowed and edematous airway. During the next six hours bronchoscopy and administration of oxygen through the bronchoscope were carried out three times. Finally, this failed to produce consciousness, and further efforts were abandoned. She expired three and a half days after operation. If tracheotomy had been

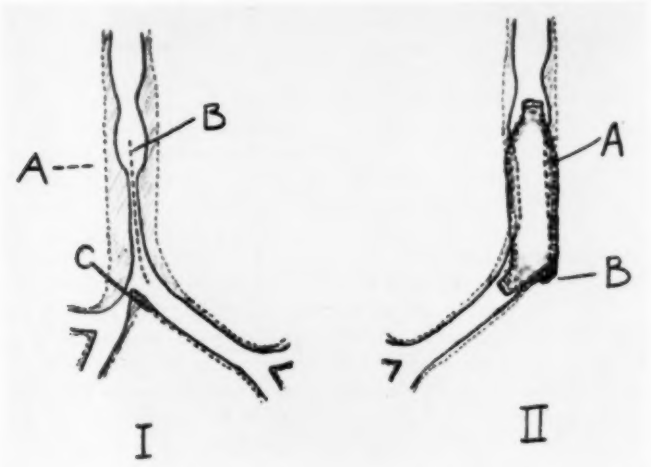

FIG. 9. Case 4. (M. I.) Drawings illustrating the operative procedure used in Case 4 (almost identical to that proposed for Case 2). I. Anterior view of tracheobronchial deformity present. A. Normal structure indicated by dotted lines. Heavy lines indicate the outline of the actual tracheobronchial lumen. B represents incision of posterior tracheal wall; C indicates level of bronchial section for right pneumonectomy. II. Posterior view of completed operation. A. Graft; B, right bronchial stump.

performed early, she might have survived. However, when first it was deemed necessary, the lower tracheal edema and edema of the left bronchial orifice called for a tube that would reach beyond this level. Such was not available.

Comment: The 32F McGill tracheal catheter was used because of the anxiety for a good airway. This is not a large size and is actually smaller than the tubes ordinarily used. It fitted the upper trachea of this patient too snugly, and its removal necessitated undue trauma which subsequently initiated all of the postoperative difficulties. It is apparently unwise, therefore, in one's zeal for a good airway, to disregard the fragility of healed tracheobronchial mucosa and not take utmost precautions to avoid trauma.

Examination of the surgical specimen revealed only atelectasis of the middle and lower lobes; the upper lobe did not contain a cavity but considerable nodular

infiltration was present in the atelectatic area. Because of active disease in the upper lobe and its bronchus, lobectomy was indicated but pneumonectomy was not warranted. The presence of two more functioning lobes may have enabled this patient to weather the postoperative difficulties. It is logical to conclude that any pulmonary resection should be ultra-conservative when it is also necessary to repair a vital airway.

Finally, a complete set of tracheotomy cannules and tubes, including extra-long sizes, should be at hand whenever tracheal surgery is undertaken.

GENERAL COMMENT

Surgical reconstruction of severe tracheal stenosis was attempted in 4 patients and succeeded in one. All of these patients had severe stenosis of the right main bronchus as well as the trachea, which is probably more than coincidence. The first 2 patients were practically hopeless surgical risks because of long-standing, severe tracheal obstruction and debility. Both succumbed at operation before the planned reconstruction could be initiated. The third patient has an excellent result with respect to the trachea. The fourth patient had a satisfactory technical result but expired after three and one-half days, mainly because of faulty surgical judgment. This experience indicates that such surgery poses as many problems for the anesthetist as it does for the surgeon. Constant, sharp attention to the airway and the patient's oxygenation, positive-negative controlled respiration, meticulous avoidance of trauma to the respiratory mucosa, and ultra-conservatism regarding the extent of necessary pulmonary resection are obligatory. In addition, a meticulous preoperative study and supportive therapy are essential. A definite operative plan should be formulated beforehand, according to careful bronchoscopic and planigraphic studies. A means of supplying controlled respiration to either lung through the chest wound should be at hand, as should a complete array of tracheotomy tubes and cannules.

CONCLUSIONS

1. Wire-enforced dermal grafts are an efficient means of treating fibrotic strictures of the bronchi.

2. Similar lesions of the trachea are also remediable with dermal grafts, but the operative procedure is more formidable because of numerous problems regarding anesthesia and the maintenance of an adequate airway. In the future, painstaking preparation, plus time and experience, will make tracheal reconstruction a more widely used procedure.

3. Defects of normal bronchial and tracheal structures produced in the experimental animal, or those resulting from acute trauma or excision of malignancies in man, may not be as receptive to dermal grafts as the thickened, fibrous walls of healed tuberculous strictures.

CONCLUSIONES

Observaciones Relativas a la Traqueoplastia

1. Los injertos dérmicos reforzados con alambre constituyen un medio eficaz de tratar las estenosis fibrosas de los bronquios.

2. Las lesiones semejantes de la tráquea son también remediables con injertos dérmicos, pero el procedimiento operatorio es más formidable debido a los numerosos problemas planteados por la anestesia y el mantenimiento de una vía aérea adecuada. En el futuro, una preparación minuciosa, unida al tiempo y la experiencia, convertirá la reconstrucción traqueal en procedimiento frecuente e inocuo.

3. Las deformaciones de los tejidos bronquiales y traqueales normales producidas en el animal de experimentación o las debidas a traumatismo agudo o a excisión de neoplasias en el hombre tal vez no resulten tan receptivas a los injertos dérmicos como las espesadas paredes fibrosas de las estenosis tuberculosas cicatrizadas, pero no debe desantenderse tal posibilidad.

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REHABILITATION OF THE TUBERCULOUS IN PHILADELPHIA[1,2]

A Study of the Effectiveness of the Program of Rehabilitation in Philadelphia for a Ten-year Period, July 1, 1939 to July 1, 1949

GERTRUDE K. LANGTON, RAYMOND D. WAGNER, AND PAUL MEIER

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INTRODUCTION

Description of the background of the project: Rehabilitation of tuberculous patients as a joint project between the Pennsylvania State Bureau of Rehabilitation, the Pennsylvania Tuberculosis Society, and the Philadelphia Tuberculosis and Health Association was initiated July 1, 1939 following a survey of Pennsylvania sanatoriums and hospitals by Mr. Holland Hudson, Director of Rehabilitation of the National Tuberculosis Association.

A special counselor was assigned to the project who devoted the first year's work to the establishment of a vocational school at Mont Alto Sanatorium and a counseling and guidance service in the Philadelphia office of the Bureau of Vocational Rehabilitation. A second counselor was subsequently assigned to the project.

At the end of a ten-year period, July 1, 1949, the project was reviewed in order to provide a complete analysis of what had been done for Philadelphia patients facing the readjustment problems created by tuberculosis and to give a general insight into the value and limitations of a rehabilitation program.

In order to obtain adequate data on what services had been rendered, a schedule was prepared to give identifying information, the medical and occupational history, and the extent and results of rehabilitation services. To obtain this information, the records in the Bureau of Rehabilitation were reviewed, not only to obtain factual material, but also to determine the cost and benefits of the program.

THE CLIENTS THROUGH THE TEN-YEAR PERIOD

Growth of program: Examination of the State Bureau of Rehabilitation records disclosed that during the ten-year period July 1, 1939 to July 1, 1949, 305 Philadelphia tuberculous patients were listed as "closed rehabilitated" after receiving services from the Bureau.

The growth of the program may be seen by the dates on which the cases were closed as rehabilitated, as shown in table 1.

In reviewing the closures, a gradual increase is noted up to 1943. The next three wartime years saw a decline. This was during the period when the special

[1] From the Philadelphia Tuberculosis and Health Association, Philadelphia, Pennsylvania.

[2] A more detailed report, including a complete history of the program, is available upon request to Miss Gertrude K. Langton, 311 S. Juniper Street, Philadelphia 7, Pennsylvania.

counselor was in military service. However, by 1947 the program returned to the previous level of activity and has continued to grow.

Composition of Group

The 305 cases included 179 white males, 108 white females, 9 non-white males, and 9 non-white females. No files were available in the Bureau office on several cases and data on many others were incomplete in several respects. This explains the many unknowns which appear in the presentation of the data.

Of the 305 cases, only 18, or 5.3 per cent, were non-white. When it is remembered that well over 33 per cent of Philadelphia tuberculous patients are non-white (1), it is obvious that the rehabilitation services are functioning less effectively for this group. As the cost to the community of non-rehabilitated tuberculosis transcends racial lines, this is a public health problem demanding

TABLE 1

Number of Clients Closed Each Year

YEAR OF CLOSURE	NUMBER CLOSED
1939	3
1940	5
1941	25
1942	31
1943	44
1944	20
1945	27
1946	14
1947	41
1948	61
1949	30
Unknown	4
Total	305

special attention. Several reasons might be suggested to explain the situation. It is highly unlikely, however, that the Negro, in view of his general occupational and educational level, has less need for rehabilitation service.

The lower educational level may influence the outcome of cases, for this study shows that in the case of the white males the lower educational levels have received less training than the higher educational levels. Rehabilitation of the lower educational levels presents a special problem.

Another, and probably the most important, factor hampering rehabilitation of the Negro group is the open or concealed discrimination by employers; to a lesser extent another factor is lack of training facilities. A health association has the duty here of pointing out the economic cost of this discrimination in terms of lowered earning power, the thousands of dollars that future breakdowns will cost, and the possible danger to public health.

Medical data: The medical forms submitted to the Bureau by the clients' physicians are the source of the data shown in tables 2 to 4.

TABLE 2

Stage of Disease on Discovery

STAGE OF DISEASE	NUMBER	PER CENT
Minimal	60	19.7
Moderately advanced	128	42.0
Far advanced	77	25.2
Pulmonary, stage unknown	24	7.9
Nonpulmonary	16	5.2
Total	305	100.0

TABLE 3

Stage of Disease on Discovery Classified by Treatment Received

TREATMENT RECEIVED	STAGE ON DISCOVERY					TOTALS
	Unknown	Minimal	Moderately Advanced	Far Advanced	Non pulmonary	
Unknown	8	11	11	4	4	38
None	1	7	1	—	6	15
Pneumothorax	6	9	67	22	—	104
Bilateral pneumothorax	2	—	6	10	—	18
Phrenic interruption	—	2	8	3	—	13
Thoracoplasty	1	—	4	18	—	23
Bed rest only	5	28	20	4	—	57
Other	1	3	6	4	6	20
Pneumothorax and phrenic interruption	—	—	3	2	—	5
Pneumothorax and thoracoplasty	—	—	2	10	—	12
Totals	24	60	128	77	16	305

TABLE 4

Clinical Classification when Accepted for Bureau Services

CLINICAL CLASSIFICATION AT SURVEY	STAGE ON DISCOVERY					TOTALS
	Unknown	Minimal	Moderately Advanced	Far Advanced	Non pulmonary	
Unknown	4	1	3	—	4	12
Improved	1	1	1	1	—	4
Quiescent	2	4	12	7	1	26
Apparently arrested	6	33	81	41	—	161
Arrested	10	19	31	28	2	90
Healed (nonpulmonary)	1	2	—	—	9	12
Totals	24	60	128	77	16	305

Table 2 shows the cases by the stage of disease at the time of discovery. It also should be mentioned that 33, or 11 per cent, of the total group had other physical disabilities which were an additional vocational handicap.

The average length of time these patients had spent in institutions was more than three years for the far advanced cases and more than one year for even the minimal cases. This serves to emphasize both the time and expense required to arrest tuberculosis and the difficulty in rehabilitating persons so long in largely idle confinement. Two hundred and forty-seven of the patients had one admission to a sanatorium, 71 had two admissions, 15 had three admissions, and one had had a fourth admission to a sanatorium. It was noted that the relapses in most cases took longer to cure than the original confinement.

The clinical methods used in treating the clients' disease are shown in table 3, and their classification at the time the Bureau accepted them for service is shown in table 4.

Type of discharge: Table 5, giving the type of discharge, shows that of the white males only 18, or 14 per cent, of the known discharges were against medical advice. Only 2, or 2 per cent, in the white females, the stage of whose disease is known, left against advice. None in the non-white group was listed as having left against advice.

TABLE 5

Type of Discharge

TYPE OF DISCHARGE	WHITE MALES	WHITE FEMALES	NON-WHITE MALES	NON-WHITE FEMALES	TOTALS
Unknown	25	5	4	2	36
With advice	112	86	4	5	207
Against advice	18	2	—	—	20
Not in sanatoriums	24	15	1	2	42
Totals	179	108	9	9	305

These data contrast sharply with the situation reported in certain Pennsylvania tuberculosis institutions. In Mont Alto Sanatorium and Philadelphia General Hospital up to 1943, more than 50 per cent left against advice. Recent figures seem to indicate that this rate has been sharply reduced.

Source of referrals: The largest source of referral was from tuberculosis sanatoriums. Hospitals, clinics, private physicians, and the Philadelphia Tuberculosis and Health Association referred most of the remainder.

Educational level: The educational level of the group is shown in table 7. It will be noted that the females had a higher general level than the males.

The educational level of the rehabilitated group was higher than that of patients in Philadelphia General Hospital, but not quite as high as those from Eagleville Sanatorium, a semi-private institution.

Services and training given by the Bureau: The Bureau's clients received several varieties of services as may be seen in table 6. Eighty-three of these clients had received both vocational training and job placement. One hundred and thirteen had also received vocational training, but had found their own jobs. Eighty clients had received no vocational training from the Bureau, but had received counseling and job-placement services. The remaining 19 clients were listed in

Bureau files as having found jobs through other means than the Bureau and had, therefore, apparently received only the counseling services that are given to all clients. Of the 289 known to be employed at the time of closure, 163 had been placed by the Bureau.

The largest part of the Bureau's effort and expense was utilized for servicing the 196 clients who received vocational training. In proportion to the number trained, a higher percentage of females received training than males, probably because males as heads of families required immediate employment. Fifty-

TABLE 6

Accomplishments of Bureau

	ATTITUDES			TOTALS
	Unknown	Yes	No	
Unknown	6	3	1	10
Trained and direct placement	32	49	2	83
Trained and indirect placement	40	68	5	113
Placement only	39	21	20	80
Counseled, indirect placement	9	3	7	19
Totals	126	144	35	305

TABLE 7

Number Trained by Education and Length of Training

LENGTH OF TRAINING	UNKNOWN	EDUCATION		TOTALS
		Less than 12 years	12 years or more	
Unknown	8	2	2	12
None	—	68	30	98
1 to 3 months	—	22	11	33
4 to 6 months	—	44	11	55
7 to 12 months	—	39	26	65
More than 12 months	1	19	22	42
Number trained	1	124	70	195
Totals	9	194	102	305

eight per cent of the white males and 25 per cent of the Negro males received training, compared to 77 per cent of the white females and 68 per cent of the Negro females.

Tables 7 and 8 show the distribution of the training by age and educational levels. These tables indicate that the younger and better educated the client, the more likely he was to receive training.

The sedentary occupations usually considered as suitable employment for the tuberculous patient generally required a higher level of education and training.

Therefore, it is rather paradoxical that the clients on the lower educational level had been receiving less training. This situation points to the need for a special approach to the problem of rehabilitating the group in the lower educational level, as it is too much to expect the counselor to overcome this handicap singlehandedly.

A general idea of the number of months required for the training of the Bureau's clients may also be gained from tables 7 and 8. The average period of training was from nine to ten months.

TABLE 8

Number Trained by Age Groups and Length of Training

LENGTH OF TRAINING	AGE GROUPS			TOTALS
	15 to 24	25 to 39	40 and over	
Unknown	9	3	—	12
None	20	57	21	98
1 to 3 months	18	14	1	33
4 to 6 months	22	30	3	55
7 to 12 months	31	31	3	65
More than 12 months	23	18	1	42
Number trained	94	93	8	195
Totals	123	153	29	305

TABLE 9

Average Months on Case Load

	NUMBER IN GROUP	AVERAGE NUMBER OF MONTHS
White males	179	19.1
White females	108	16.0
Non-white males	9	27.5
Non-white females	9	20.1
Totals	305	18.3

Table 9 shows the average length of time in months that the Bureau's clients were a part of the case load.

Of the 196 clients receiving training, only 11 discontinued their course before completion. Two had suffered a relapse of their tuberculosis while the others interrupted training for various personal reasons, including the desire to get immediate employment and difficulties at school.

Cost of program: The total direct cost to the Bureau of the 227 cases which required direct expenditures was $92,603 throughout the entire ten-year period. Most of the other 78 clients were receiving counseling and placement services involving no direct costs. Administration costs came out of the Bureau's general

funds, tuberculosis work being approximately 10 per cent of their activities for vocational rehabilitation of the handicapped.

As table 10 shows, the actual direct cost averaged $408 for each of the cases getting financial aid. Fifty thousand and nine hundred dollars was used to pay tuition for 131 clients, and $41,693 was spent on maintenance, transportation, and supplies.

Wages before and after rehabilitation: The most satisfying evidence of the economic benefit of rehabilitation is shown in tables 11A and 11B which contrast the wages earned by the clients before and after their rehabilitation.

TABLE 10

General Cost of Training

	WHITE MALES	WHITE FEMALES	NON-WHITE MALES	NON-WHITE FEMALES	TOTALS
Number in group	179	108	9	9	305
Number who received aid	124	93	4	6	227
Total cost for all cases	$56,539.00	$30,883.00	$2,381.00	$2,800.00	$92,603.00
Average cost for all cases	$ 455.96	$ 332.08	$ 595.25	$ 466.67	$ 407.94
Number of examinations	50	24	1	3	78
Total cost	$ 632.00	$ 319.00	$ 10.00	$ 35.00	$ 996.00
Average cost	$ 12.64	$ 13.29	$ 10.00	$ 11.67	$ 12.77
Number receiving transportation and maintenance	88	67	2	4	161
Total cost	$19,518.00	$10,738.00	$ 962.00	$ 957.00	$32,175.00
Average cost	$ 221.80	$ 160.26	$ 481.00	$ 239.25	$ 199.84
Number of tuitions paid	96	27	3	5	131
Total cost	$30,450.00	$17,902.00	$1,140.00	$1,408.00	$50,900.00
Average cost	$ 317.88	$ 663.04	$ 380.00	$ 281.60	$ 388.55
Number receiving other items	94	83	2	6	185
Total cost	$ 6,561.00	$ 2,243.00	$ 279.00	$ 435.00	$ 9,518.00
Average cost	$ 69.80	$ 27.02	$ 139.50	$ 72.50	$ 51.45

Before they received Bureau services, more than 94 per cent of the white, and all non-white clients, were unemployed. The few who were working, often on jobs which were quite unsuitable for the tuberculous, averaged only $20.50 weekly for the males and $16.83 for the females. The wages were inadequate for the standards of diet and living conditions required by former patients in a tuberculosis sanatorium.

Considering the situation at the time the cases were closed, however, a startling improvement is evident. At least 94 per cent of the white males and 97 per cent of the white females were employed[3] and average earnings were $34.35

[3] One white male died, and the wages of 15 patients were not reported.

and $24.85, respectively. The non-white males, 89 per cent employed, were averaging $24.00 weekly, while the 78 per cent of the non-white females employed earned an average weekly salary of $30.00.

TABLE 11A

Average Wage before Rehabilitation

	WHITE MALES				WHITE FEMALES			
	Age			All Ages	Age			All Ages
	15 to 24	25 to 39	40 to 60		15 to 24	25 to 39	40 to 60	
Number of cases	67	88	24	179	49	56	3	108
Number working	2	8	—	10	3	3	—	6
Per cent working	3.0	9.1	—	5.6	6.1	5.4	—	5.6
Total earned	$41.00	$164.00	—	$205.00	$50.00	$51.00	—	$101.00
Average for those working	$20.50	$ 20.50	—	$ 20.50	$16.67	$17.00	—	$ 16.83

Note: All 18 non-white clients were unemployed before rehabilitation.

TABLE 11B

Average Wage at Closure

	WHITE MALES				NON-WHITE MALES			
	Age			All Ages	Age			All Ages
	15 to 24	25 to 39	40 to 60		15 to 24	25 to 39	40 to 60	
Number of cases	67	88	24	179	4	4	1	9
Number working	61	83	24	168	3	4	1	8
Per cent working	91.0	94.3	100.0	93.9	75.0	100.0	100.0	89.0
Total earned	$1,968.00	$2,950.00	$852.00	$5,770.00	$96.00	$74.00	$22.00	$192.00
Average for those working	$ 32.26	$ 35.54	$ 35.50	$ 34.35	$32.00	$18.50	$22.00	$ 24.00
	WHITE FEMALES				NON-WHITE FEMALES			
	Age			All Ages	Age			All Ages
	15 to 24	25 to 39	40 to 60		15 to 24	25 to 39	40 to 60	
Number of cases	49	56	3	108	3	5	1	9
Number working	48	54	3	105	2	4	1	7
Per cent working	98.0	96.4	100.0	97.2	66.7	80.0	100.0	78.0
Total earned	$1,207.00	$1,343.00	$ 59.00	$2,609.00	$43.00	$144.00	$23.00	$210.00
Average for those working	$ 25.15	$ 24.87	$ 19.67	$ 24.85	$21.50	$ 36.00	$23.00	$ 30.00

Since the above averages were computed over ten years, the inflationary tendency of this period limits the application of the data. They are suitable, however, for comparative purposes. Considering the high prices of the war and postwar years which the program covered, the average wages, while a big improvement, could not have been adequate for a safe standard of living in many cases.

The importance of the income of ex-patients can be seen when it is realized how many support other persons as well as themselves. Table 12 shows the marital status of the clients and reveals that 61 of them had dependents totaling 132 in number.

Occupational status: A comparison of the type of job held by the clients before they received the Bureau of Rehabilitation services with their type of employment afterwards shows a significant improvement in their general occupational level. This is shown in a shift from the less skilled categories of labor to skilled, technical, and clerical employment. A corresponding increase in income and job security and a decrease in strenuous labor may be assumed.

TABLE 12

Marital Status of Clients and Number with Dependents

MARITAL STATUS	MALE	FEMALE
Unknown	9	1
Married	46	10
Single	124	93
Divorced	2	1
Widowed	1	6
Separated	6	6
Totals	188	117
NUMBER OF DEPENDENTS	**MALE**	**FEMALE**
Unknown	8	1
None	128	107
One	20	7
Two	13	2
Three	9	—
Four	6	—
Five	1	—
Six	2	—
Seven	1	—
Total number with dependents	52	9

The type of training objective most frequently found in the male group was clerical and business employment. Varied types of skilled labor came second, closely followed by various crafts of a semi-professional or technical nature, such as drafting or watch repairing.

Among the female group, more than two-thirds were trained for clerical work, with beauty culture and other semi-professional and skilled crafts accounting for most of the remainder. Five males and 2 females were trained for professional objectives. In many cases, the productive power of the individual has been increased by his training far above his pre-tuberculosis level.

The question of exactly what jobs were filled will not be considered in this

discussion. It is not within the scope of this paper to consider which jobs are suitable for ex-patients, and other literature on this problem is available. Moreover, it is doubtful if a mere listing of job titles would be of much benefit, since practical experience in vocational counseling shows that too often titles have only incidental relation to the many health factors involved on a job, i.e., the hours spent working and in traveling to and from work, intensity of effort, adequate pay, healthy location, and the adaptability of the clients to the work.

At present, much depends on the judgment of the counselor, physician, and the client himself. To what extent scientific measurement of strain and medical supervision of ex-patients is possible in the existing industrial and business world is uncertain and should be the topic of much further study.

TABLE 13A

Occupational Status before and after Rehabilitation (Complete Group)

OCCUPATIONAL STATUS	MALE		FEMALE	
	Before Rehabilitation	After Rehabilitation	Before Rehabilitation	After Rehabilitation
Unknown	12	7	4	1
None	29	1	31	—
Professional	1	5	5	2
Technical and semi-professional	7	30	7	16
Clerical, sales, and business	32	65	28	79
Skilled and semi-skilled labor	58	52	14	11
Repairs and maintenance	5	13	—	—
Personal services	1	—	9	1
Agriculture	—	1	—	—
Housewife	—	—	—	4
Unskilled labor	43	14	19	3
Totals	188	188	117	117

Employers do not hire labor for purposes of charity, so no matter what field the ex-patient selects, he must expect to work with the intensity of effort that competitive conditions demand of healthy workers. The problem thus becomes one of selecting occupational fields in which the workers in general enjoy conditions presenting no threat to health. This is likely to be a social problem reaching beyond the limitations of a health agency.

Change of occupation: Table 13A, a comparison of the job classifications of clients before they received Bureau services with their job classifications afterward, shows the changes made through the rehabilitation program. Improvements are greatest among the clients who received vocational training from the Bureau, as shown in table 13B.

The cases of only 23 persons were closed on the grounds of employment on the same jobs they had had previous to having tuberculosis. In these cases, the Bureau had simply acted as a placement service aiding the clients to recover

their old jobs. But in 267 cases new jobs had to be found, and in 199 cases this meant training the ex-patients for new occupations.

In fact, 60 younger clients had never worked in any full-time employment and these in particular required training. The other clients had had jobs which were considered unsuitable for persons with tuberculosis. This was especially true in regard to the unskilled laborers, although several clients had to be transferred from professional work that was too strenuous physically. Vocational rehabilitation attempted to place or train them in occupations less threatening to their health.

TABLE 13B

Occupational Status before and after Rehabilitation (Trained Group)

OCCUPATIONAL STATUS	MALE			FEMALE		
	Before Rehab.	Training Objective	After Rehab.	Before Rehab.	Training Objective	After Rehab.
Unknown	2	—	—	2	—	—
None	21	72	1	29	24	—
Professional	1	5	5	4	2	2
Technical and semi-professional	4	30	25	3	18	14
Clerical, sales and business	19	37	37	20	67	64
Skilled and semi-skilled labor	32	30	32	9	4	3
Repairs and maintenance	2	5	4	—	—	—
Personal services	—	—	—	5	—	—
Agriculture	—	1	1	—	—	—
Housewife	—	—	—	—	1	3
Unskilled labor	24	—	—	14	—	—

PRESENT STATUS OF CLIENTS

In order to determine the present status of the Bureau's former clients, a brief questionnaire was mailed to each of them requesting information on type of job, wages, and number of months employed or unemployed. Medical information was also requested to determine: (a) the number who had suffered a relapse; (b) at what interval after training; and (c) whether they were now at home or in a hospital or sanatorium. As could be expected there had been many changes over the ten-year period. Some did not reply, while changes of address of others had caused them to disappear from the records of the local clinics. Almost 65 per cent did answer, however, and provided us with some helpful information on their status as of July 1, 1949.

Table 14, the job classification of the clients, shows the distribution of those answering to be roughly similar to the distribution of closed job classifications. There is one big exception: the white females who reported marriage and a change of occupation to housewife. Forty-four per cent of the white males, 45 per cent of the white females, and 33 per cent of the non-white males reported that they were still employed in their rehabilitated jobs. Eleven per cent of the white males and 9 per cent of the females reported related occupations. This indicated

that the majority of the group were still using the skills acquired during their rehabilitation program. Nineteen white females were housewives; 20 of the white males, 2 of the non-white males, and one of the white females were working at occupations unrelated to their rehabilitated jobs.

Tables 15 and 16 show the present weekly wage of the clients who answered the questionnaire, as well as the average number of months they have been employed since their rehabilitation.

TABLE 14

Present Job Classification

JOB CLASSIFICATION	WHITE MALES	WHITE FEMALES	NON-WHITE MALES	NON-WHITE FEMALES
Unknown	68	34	3	3
None	29	14	2	5
Professional	3	2	—	—
Technical or semi-professional	17	2	1	—
Clerical, sales, and business	28	32	1	—
Skilled and semi-skilled labor	23	1	1	—
Repairs and maintenance	6	—	—	—
Personal services	—	1	1	—
Agriculture	—	—	—	—
Housewife	—	21	—	1
Unskilled labor	5	1	—	—
Totals	179	108	9	9

TABLE 15

Present Job—Weekly Wage

	NUMBER IN GROUP	NUMBER REPORTED WHO HAVE WORKED	TOTAL WEEKLY WAGE	AVERAGE WEEKLY WAGE
White males	179	71	$3,302.00	$46.51
White females	108	35	1,208.00	34.51
Non-white males	9	4	128.00	32.00
Non-white females	9	—	—	—
Totals	305	110	$4,638.00	$42.16

The less satisfactory side of the program is shown in tables 17 and 18. About 13 per cent of the clients reported themselves unemployed for an average of more than twelve months. Unemployment among the Negroes was greater than among the whites, although of a more recent date. Many of these clients have asked the Bureau to help them again, so their cases have been reopened and are on the current case load. The problem of unemployment is a serious one for the Bureau, for it makes placement of new clients more difficult and is a threat to the health of old ones. In this case, the Bureau's ability to serve its clients is greatly hampered by the economic situation.

In table 18 it may be seen that 14 per cent of the clients have suffered a relapse at a time averaging about twenty-seven months after their cases were closed in the rehabilitation office. This raises the question of what was the cause of their relapse, whether they had been permitted to work too early, had failed

TABLE 16

Average Months Employed of Those Who Have Worked Including Only Those Who Answered Questionnaire

	NUMBER IN GROUP	NUMBER REPORTED WHO HAVE WORKED	TOTAL NUMBER OF MONTHS	AVERAGE NUMBER OF MONTHS
White males	179	103	3,482	33.81
White females	108	65	2,064	31.75
Non-white males	9	5	137	27.40
Non-white females	9	5	69	13.80
Totals	305	178	5,752	32.31

TABLE 17

Unemployed—Average Months for Those Now Unemployed

	NUMBER IN GROUP	NUMBER REPORTING	NUMBER UNEMPLOYED	TOTAL MONTHS	AVERAGE MONTHS
White males	179	108	14	179	12.8
White females	108	74	7	105	15.0
Non-white males	9	6	1	2	2.0
Non-white females	9	6	4	31	7.8
Totals	305	194	26	317	12.2

TABLE 18

Relapse of Tuberculosis—Months After Closure

	NUMBER IN GROUP	NUMBER REPORTING	RELAPSES	AVERAGE NUMBER OF MONTHS
White males	179	112	17	28.0
White females	108	72	10	25.3
Non-white males	9	6	—	—
Non-white females	9	6	1	—
Totals	305	196	28	27.0

to take reasonable care of themselves, or had had unsatisfactory working or living conditions. As was remarked earlier, vagueness of job titles and lack of medical supervision of employment make the last problem a difficult one to solve.

It can be deduced, however, that the number of relapses of tuberculosis among the clients after rehabilitation has been considerably less than the same group had before receiving Bureau services.

It was believed that it would be interesting to ask the former clients the question, "Do you feel the Bureau really helped you?" in order to judge their attitude toward the program. It was realized that no organization operating on a large scale can hope to satisfy all of its clients, and the Bureau is no exception. There are always numerous persons who feel that more should have been done and it is not always possible to provide real help for everyone. Nevertheless, more than 80 per cent of the 179 persons answered the question in the affirmative, and many wrote spontaneous, enthusiastic letters telling how much rehabilitation had done to improve their lives.

How the question was answered by the clients is shown in table 6, together with what Bureau services they had received, and the latter was found to be a decisive factor in the proportion of unsatisfied clients. Only 2 of the 83 clients reporting who had had both training and placement services answered "No;" but of the 19 persons who had received neither training nor jobs from the Bureau, but only counseling, 12 answered "Yes" and 7, "No." To what extent the negative answers were justified is another question. Some had not received jobs in fields to which they aspired, an outcome not always the fault of the Bureau. Others seemed unaware of the fact that the Bureau had paid part of their tuition, while a few seemed, by the Bureau's own records, to have received little actual attention.

DISCUSSION

The economic benefits to Philadelphia of vocational rehabilitation of the tuberculous have been very satisfactory. The alternatives to rehabilitation may be a higher rate of relapse, costing approximately $10,000 each (2); or a large number of unemployed receiving relief from public funds for themselves and their dependents. The cost of the latter was shown in a study of the case load of the Philadelphia Department of Public Assistance in October 1948, which revealed that 600 tuberculosis patients in Philadelphia were then receiving supplemental assistance in addition to their regular relief grants. The regular monthly relief grant for the ten-year period in our report varied from $10.26 per month per person in 1939 to $29.16 per month per person in 1948; and in October 1948 the Department of Public Assistance was spending $4,400 per month for supplementary grants to tuberculosis patients.

Against this high cost of tuberculosis is contrasted the success of the rehabilitated patients, who have been changed from "tax consumers to tax payers," and are now earning more, in many cases, than they did before their illness. The average Philadelphia client has already earned about $6,000 in the comparatively short time since he was closed as rehabilitated.

All this, when contrasted with the program's cost of slightly more than $400 per client, should be convincing evidence that not only is the rehabilitation program a very wise and profitable investment of public funds, but that any

weaknesses or gaps in the program are a continuing expense and danger to the community. This may be stated without attempting to weigh, in monetary terms, the social and economic benefits to the individual patient and his neighbor.

Only after understanding the necessity and the benefits of the program can we proceed to a critique of the previous work, which would aid us in expanding it and filling in the gaps.

First it must be remembered that the work of the rehabilitation bureau is always limited by the social context in which it operates. This report has mentioned problems which are a dangerous and expensive health threat to the community, and which are basically beyond the Bureau's powers. These problems are unemployment, poor working conditions, racial discrimination, and the failure of legislatures to allocate adequate funds for public health and rehabilitation purposes. Tuberculosis infections, breakdowns, and relapses traceable to these causes cannot be fairly blamed on the work of the tuberculosis agency, for improvements in the economic, social, and political situation are a problem for the whole community.

Keeping in mind the benefits and limitations of the whole program, we can now turn to some critical remarks on the program. The greatest weakness observed in the ten-year program was the proportion of the tuberculous ex-patients served. The Bureau of Vital Statistics of the Philadelphia Department of Health stated that 2,893 new cases of tuberculosis were reported in the fiscal year 1948. No doubt, some of the new cases fell victim to the mortality rate and others can return to suitable previous occupations; but how many could benefit by Bureau services? If the proportion is at all large, then 305 closed cases for a ten-year period in Philadelphia is quite a modest start toward filling the total need. Experience shows, that the number of referrals greatly exceeds the cases closed, as many prove to be ineligible or unsuitable for service for various reasons.

Two estimates of the proportion of tuberculosis cases requiring rehabilitation are available to us. Kiefer quotes a Federal Office of Vocational Rehabilitation Survey of the vocational needs of 1,463 clients in the Saranac Lake area in 1945 to 1946 (2). This reasonably large sample showed that 40.7 per cent needed training, 16.7 per cent more needed only direct placement, and 20 per cent required sheltered employment. Of the remainder, 9.6 per cent were housewives, 9.6 per cent required continuous medical care, and the needs of 3.4 per cent were not reported. This indicates that the great majority of clients would benefit by rehabilitation services.

Unfortunately, the only survey of this problem in the Philadelphia area was the survey by Harrington and Wagner in 1947 of the needs of 180 patients at the Eagleville Sanatorium, a semi-private institution (3). This study indicated that 60 per cent of the patients had no satisfactory jobs to return to, although as large a percentage would have to be self-supporting. Fully 50 per cent, in fact, had no idea as to what they would do when they left the Sanatorium, and 40 per cent regarded their previous occupations as too strenuous.

If either of these estimates are relevant to the needs of Philadelphia tuber-

culosis patients as a whole, and there seems no reason to believe otherwise, then it is apparent that a much larger percentage of patients should benefit by rehabilitation services. To reach and help the group which needs this service, it is necessary to increase greatly the number of patients referred to the Bureau of Rehabilitation, and to strengthen the Bureau's tuberculosis program.

In order to increase the number of referrals to the Bureau, and to improve the program, it is necessary to continue to educate the medical staff of tuberculosis institutions as well as general medical and social agency personnel. Strengthening the rehabilitation program requires the support of the official and voluntary agencies in augmenting the personnel and funds of the Bureau itself, extension of the program to the in-sanatorium phase, and the development of special approaches to the most difficult problems.

If the case load is to be greatly enlarged, then it is necessary to increase the number of counselors and maintain the Bureau's budget to meet all essential needs. In 1948, when adequate funds were not available, the Bureau of Rehabilitation training programs were canceled and maintenance allotments reduced, causing unnecessary hardships and the loss of confidence by clients needing the Bureau's services. This experience should not be repeated if rehabilitation is to continue on a sound basis.

In this study we have seen a lack of training for two particular groups which need to be given consideration, the clients on the lower educational level and those in the non-white group. Since these clients need suitable employment in order to prevent breakdowns, consideration should be given to developing plans to ensure these people the full benefits of a rehabilitation program.

The program discussed so far has been almost entirely on a post-sanatorium basis. However, there is now a definite feeling in rehabilitation circles that this service should be extended to patients during their sanatorium experience. As early as 1938, Mr. Hudson quotes Dr. William Turnbull (4), who was at that time medical director of Philadelphia General Hospital and former medical director of Cresson State Sanatorium, as saying "the time and place to select patients for rehabilitation was during sanatorium treatment, a time which affords revealing glimpses of character, attitudes, hazards of assets as well as an inside story of physical possibilities, which can rarely be obtained as satisfactorily after the discharge of the patient."

Certainly, vocational aptitude and work tolerance can be better determined in the sanatorium, where medical changes can be observed on a day-to-day basis and sufficient time given to evaluate the patients' possibilities. This is superior to relying on a single day's testing and one or two interviews, which is the general practice at the present time. The unhurried sanatorium atmosphere lends itself to a more objective evaluation of the patient's future by freeing the patient of much of the emotional conflict aroused by the one-day test.

Our first local experience with an in-sanatorium program was one developed at Eagleville Sanatorium by two rehabilitation students at the University of Pennsylvania (3). Convinced by their own sanatorium experience at this institution that there was fruitful ground there for a pre-vocational training program,

they offered to devote their free time during the summer months to a study of this problem. With funds supplied by the Pennsylvania Tuberculosis Society, the Philadelphia Tuberculosis and Health Association, and the board of the institution, a program was developed including four pre-vocational courses, enlargement of the institutional book and record library, and an analysis of the patients' rehabilitation needs. From this project we learned:

1. That 52 per cent of the patients expressed an interest in some type of in-sanatorium training.
2. That 33 per cent desired vocational training, while 9 per cent wanted to complete their high school education.
3. That 10 per cent of the patients wanted courses of a cultural and academic nature and such a program proved successful on a small scale during that summer. The courses given were on civics, literature, and music.
4. It was agreed by the interested agencies that a resident rehabilitation counselor could do much in providing vocational counseling and testing, and arranging courses of a vocational nature.
5. That activity assigned to ambulatory patients should be selected with a view to pre-vocational training.
6. That a sizable library of books and recorded music was a useful therapeutic measure.
7. That in-sanatorium educational activity improved patients' morale and mental confidence, and prevented them from losing their initiative and ambition.

As the report of the project stated:

> One of the tragic aspects of tuberculosis is the time it wastes in the lives of people, especially those young people whom it afflicts. In every sanatorium, the majority of men and women are enduring many monotonous days which might be spent in pleasant activities of a vocational or cultural nature. The effects of this dreary existence go further than the loss of precious years. As Doctor Kiefer has said: 'In some patients an unavoidable psychological state which is detrimental to progress may result. Such patients become increasingly dependent on the sanatorium, and even fear to resume an active place in society.'

Although these recommendations received general approval, a permanent program failed to develop at this institution due to a lack of funds and properly trained personnel. However, following this demonstration, a program was developed at Mont Alto Sanatorium by the Pennsylvania Tuberculosis Society which will benefit many Philadelphia patients. This program began December 1947 with the appointment of a full-time rehabilitation director at this institution. The employment of a social worker and an occupational therapist has augmented this program and results will probably be reported at a later date.

Our experience has also shown that rehabilitation is a large and comprehensive field. It embraces health, education, occupational therapy, guidance, the Social Services, recreation, and employment. Each field has its own contributions to make, but they are valueless unless they are correlated with the contributions of their co-workers. Rehabilitation is a team process, and the closer the cooperation between the voluntary and the public agency, the more effective will be the program.

SUMMARY

An analysis has been made of the background and disposition of 305 tuberculous patients, listed as "closed rehabilitated" cases in the Philadelphia office of the Bureau of Rehabilitation from July 1, 1939 to July 1, 1949. The purpose of the study was to evaluate the rehabilitation program initiated as a joint project of an official and a voluntary agency.

The criteria for referral to the Bureau were arrested disease with satisfactory prognosis, educational background, and intelligence showing promise of successful employment. Discharge from the sanatorium against medical advice did not disqualify a patient from Bureau services. Nearly 10 per cent of those studied fall in this category. The success of the rehabilitation program was less in this group, however, than in those discharged with medical advice.

Of the 305 cases studied, only 5.3 per cent were non-white, while 33 per cent of the reported cases of tuberculosis in Philadelphia in 1948 were in the non-white group. We are not in a position to determine whether this reflects the poorer prognosis or the difficulty in finding training and placement facilities for the non-white group. Generally speaking, those who were younger than thirty years and of a higher educational level received better training and more satisfactory placement, as measured by current income.

The direct cost to the Bureau for each patient receiving financial aid averaged $408. As tuberculosis rehabilitation is a small part of a larger program, it is difficult to estimate administration costs.

It is believed that despite certain limitations, the program of rehabilitation of the tuberculous in Philadelphia has proved a wise investment, and there is at present concrete evidence that the program is being expanded.

SUMARIO

Rehabilitación de los Tuberculosos en Filadelfia

Este estudio versó sobre los antecedentes y destino de 305 tuberculosos, rotulados como casos terminados, rehabilitados en la filial de Filadelfia de la Oficina de Rehabilitación, del 1° de julio de 1939 al 1° de julio de 1949. El análisis tenía por objeto justipreciar el plan de rehabilitación iniciado como obra conjunta por un organismo oficial y otro cívico.

Las pautas que gobernaron el envío de los enfermos a la Oficina consistieron en estacionamiento de la dolencia con pronóstico satisfactorio, buenos antecedentes educativos e inteligencia indicativa de éxito en el empleo ofrecido. El alta del sanatorio contra el consejo del médico no privaba al enfermo de los servicios de la Oficina. Aproximadamente 10 por ciento de los estudiados corresponden a esta categoría; pero el éxito del plan de rehabilitación fué menor en este grupo que entre los dados de alta por consejo del médico.

De los 305 casos estudiados, sólo 5.3 por ciento no eran blancos, en tanto que 33 por ciento de los casos de tuberculosis comunicados en Filadelfia en 1948 correspondían a este grupo. Los AA. no se encuentran en aptitud de determinar si esto refleja un pronóstico peor o mayor dificultad para encontrar medios de adiestramiento y colocación para los no blancos. Hablando en general, los sujetos

de menos de treinta años y de superior educación recibieron mejor adiestramiento y puestos más satisfactorios desde el punto de vista de ingresos económicos.

El costo directo a la Oficina por cada enfermo que recibió ayuda económica promedió 408 dólares. Como la rehabilitación de los tuberculosos sólo representa una pequeña parte de un plan más vasto, resulta difícil calcular los gastos de administración.

Parece que, a pesar de ciertas limitaciones, el plan de rehabilitación de los tuberculosos en Filadelfia ha resultado ser una inversión acertada, y ya hay pruebas concretas de que va a ser expandido.

Acknowledgment

Grateful acknowledgment is made to the manager of the Philadelphia Bureau of Rehabilitation, Mr. R. Cavaliere, and the special counselors for the tuberculous, Mr. R. Ivan Shrader and Mr. Robert Fallon, for submitting their records for this study and for their assistance in evaluating the replies to the questionnaire. Mr. Shrader was also responsible for drafting and signing the letters which were sent to individual clients.

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Case Reports

MILIARY TUBERCULOSIS AND PREGNANCY[1]

GEORGE E. SPENCER, PASCAL D. SPINO, AND J. D. SILVERMAN

(Received for publication January 23, 1950)

The combination of pregnancy and miliary tuberculosis must be unusual, as a search of recent literature fails to reveal any cases. Accordingly, the following case is reported as an example of the coexistence of these two entities.

CASE REPORT

A 23-year-old white female was admitted to the Tuberculosis League Hospital, Pittsburgh, Pennsylvania, on July 10, 1947. Her first symptoms occurred in May 1947, with an acute onset of chills and a temperature to 102° F. She was treated with sulfonamide therapy and apparently made a good recovery in a few days except for fatigue and shortness of breath. In March and April, the patient had morning nausea; in June, after her acute illness, she consulted an obstetrician who found her to be about three months' pregnant. Because of continuing tiredness and fever, however, he referred her to an internist for examination. A roentgenogram of the chest revealed miliary lesions in the lung, although the sputum was negative for tubercle bacilli. Streptomycin was begun on June 25, 1 gm. daily, and was continued until time of admission to the hospital. At the time of admission the patient stated that she felt much better. On admission, she was noted to be in no apparent distress, although somewhat flushed and perspiring freely. Physical examination of the chest was noteworthy for a complete lack of abnormal signs. The uterus could be felt at the umbilicus; the fetal heart tones were audible. Neurologic examination revealed no abnormalities. A slight scoliosis was noted in the dorsal spine. A roentgenogram of the chest showed "snowstorm stippling" of both lung fields, typical of miliary tuberculosis. The sputum was negative for tubercle bacilli on admission and during her entire stay in the hospital; acid-fast bacilli were detected in the sputum on only one occasion, in January 1948. However, direct smears of urine were repeatedly positive for acid-fast bacilli, and there were many white cells in the urine. The family history and contact history were negative for tuberculosis.

On July 30 the patient spontaneously went into labor and a short time later was delivered of a living, female child of approximately five and one-half months' gestation. The child lived approximately thirty minutes after delivery. The placenta showed numerous caseous miliary tubercules and tubercle bacilli were isolated from these. An autopsy was obtained on the child, but no evidence of tuberculosis was found in any of the organs.

Post partum, the patient was given estrogen therapy to suppress lactation, and had no obstetrical complications. She stated that she breathed much easier, and she began to show steady improvement. By October 1947, the lesions in the lung were beginning to disappear. The patient was much improved clinically. Examination of the cerebrospinal fluid at that time showed 34 cells per cu. mm.; culture and smear of the fluid were negative. Streptomycin was discontinued November 5, after the patient had received 236 gm. At that

[1] From the Tuberculosis League Hospital, Pittsburgh, Pennsylvania.

time, the patient was out of bed and around the ward and felt quite well. Both lungs appeared to be completely clear on roentgenographic examination.

Shortly after Christmas, however, the patient complained of severe headache, stiffness of the neck, and a low-grade fever. The cell count in the cerebrospinal fluid rose to 178 cells which were predominately lymphocytes. She was again placed on intramuscular streptomycin and 100 mg. of intrathecal streptomycin twice weekly were also administered.

FIG. 1. Roentgenogram taken July 18, 1947, illustrating lesions.

In February, for the first time she began to show evidence of streptomycin toxicity, with tinnitus and deafness particularly noted. There was also some instability of gait. The cerebrospinal fluid cell count remained elevated between 200 to 350 cells per cu. mm., but by May the patient was feeling so much better that she was sitting up ten minutes daily. Headaches had disappeared, and by July her cerebrospinal fluid cell count had dropped to 44 cells per cu. mm. She was up about fifteen minutes daily. Between December 1947 and May 1, 1948, the patient received 258 gm. of streptomycin, and no further drug was given until August 16. At this time she again developed severe headaches with nausea, vomiting, blurring of vision, nuchal rigidity, and dizziness. The cerebrospinal fluid pressure was elevated to 300 mm. of water and 156 lymphocytes per cu. mm. were present. The patient's

condition deteriorated slowly and an occasional direct smear of the cerebrospinal fluid now revealed acid-fast bacilli. She showed a temporary improvement in November and December, however, but symptoms returned in January 1949. At this time she was placed on PAS but could not tolerate it and vomited most of the drug. She slowly became vegetative. The cerebrospinal fluid became yellowish and was positive for acid-fast bacilli. A bilateral

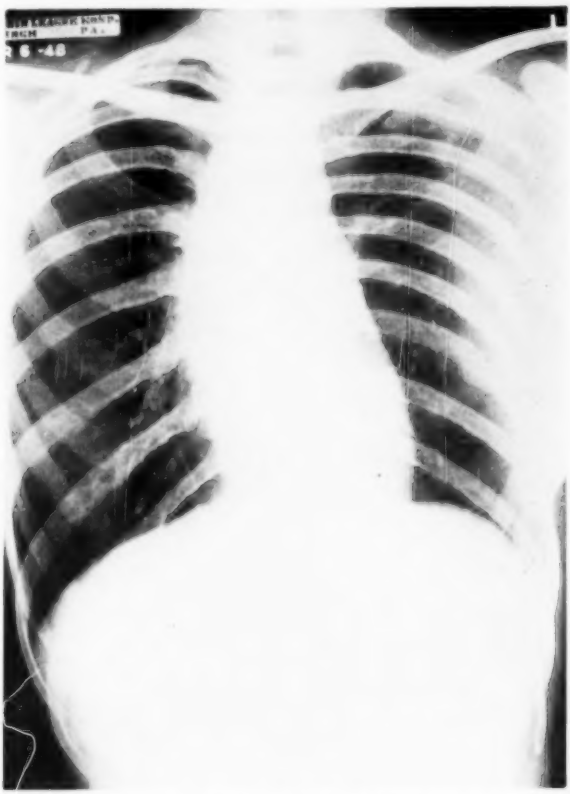


FIG. 2. Roentgenogram taken April 1948, showing lungs free of miliary lesions.

ankle clonus developed; nuchal rigidity became marked; there was almost complete loss of hearing and vision; and the patient died April 14, 1949.

An autopsy was performed which showed tuberculous meningitis, tuberculous pyelonephritis with large tuberculous abcesses in the kidneys, and healed miliary lesions in the lungs. An examination of the brain at autopsy revealed a tubercle in the right parietal lobe with miliary tubercles in the choroid plexus. Roentgenograms of the patient's chest had revealed no evidence of disease for more than a year. She had received a total of 725 gm. of streptomycin between July 1947 and April 1949. She also received 16 gm. of PAS daily for one month, most of the drug being lost through vomiting.

COMMENT

This case is noteworthy for the combination of pregnancy and miliary tuberculosis, which must be a rare occurrence. In addition, at autopsy a tuberculous pyelonephritis was found, although this had been suspected because of persistently positive urine cultures.

It seems likely, in view of the normal autopsy findings in the infant, that, if tuberculosis had occurred later in the pregnancy, a normal, surviving infant may have resulted.

SUMMARY

A case of miliary tuberculosis and pregnancy is presented, with spontaneous premature birth of a living infant. The mother then recovered from her miliary pulmonary disease, only to die later of meningitis and pyelonephritis.

SUMARIO

Granulia y Embarazo

En el caso descrito, había granulia y embarazo, con nacimiento prematuro espontáneo de un feto vivo. La madre se repuso después de su neumopatía miliar, pero sólo para morir más tarde de meningitis y pielonefritis.

ERODING CALCIFIED MEDIASTINAL LYMPH NODES[1,2]

SHEA HALLE AND OSCAR BLITZ

(Received for publication January 19, 1950)

Calcified tuberculous lymph nodes in the mediastinum have long been recognized as a source of potential disease in adults. These nodes not infrequently act like foreign bodies and seek entrance into body lumina to be extruded. Thus tracheobronchial nodes may erode into any part of the respiratory tract. In the past this course of events is usually reviewed in retrospect when bronchial tree calcifications are coughed up or removed bronchoscopically. Occasionally it is first diagnosed following lobectomy for atelectasis with or without a suppurative process distal to the obstruction of a bronchial lumen compressed by an adjacent lymph node. Recently the writers have observed two cases of calcified tuberculous lymph nodes which were diagnosed early in the course of events before the erosion process had caused complete perforation. It is believed that these cases are of general interest at this time because awareness of the syndrome will aid in the early diagnosis of various respiratory symptoms, e. g., hemoptysis, chest pains; and because modern chest surgery will allow for removal of calcified nodes that are threatening because of erosion.

Case 1. A 30-year-old white male was admitted to this hospital on April 20, 1948. He had been well until December 1944, when he noted the onset of very sharp persistent pains which could be felt beneath the sternum, anteriorly, and in the mid-back, posteriorly. Because of these pains the patient was evacuated from the theater of operations and discharged from the Army. He returned to his occupation, which was painting, and got along well for about eight months, at which time he went to a Veterans Administration hospital complaining again of severe, intermittent pain in the middle of the back and under the sternum. The pain was more severe with respiration. He complained of occasional fever and some weight loss. He was thoroughly examined and was told that he had calcified nodes in the mediastinum which were responsible for his pain. While in the hospital his symptoms subsided, and he was discharged.

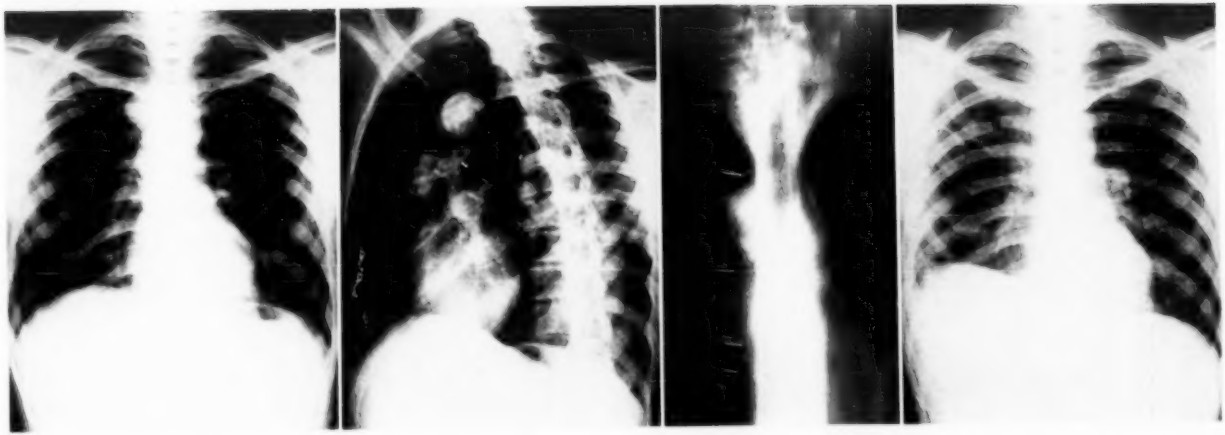
He remained well until ten days before admission to this hospital three years later, at which time he suffered from recurrent bouts of hemoptysis. He also complained of nausea, weakness, a ten-pound weight loss, occasional mild, nonproductive cough, and night sweats about once a week for the preceding year. The patient complained bitterly about the aching and sharp pain in the sternal area, worse on inspiration.

Physical examination was essentially negative. He was found to be a well-developed, well-nourished, white male, who did not appear to be ill.

Course in hospital: A roentgenogram of the chest revealed a zone of infiltration in the right third anterior interspace overlying the adjacent third rib. There was a calcific focus within this infiltration which had the appearance of Ghon tubercle (figure 1). In the right mediastinal region two calcific masses could be identified. Calcification within these masses was of stippled quality, the type usually seen in calcifying tuberculous nodes. One was oval and in the anterior mediastinum adjacent to the right main stem bronchus; the other mass was superior, contiguous with the trachea just above the bifurcation (figure 2).

[1] From the Veterans Administration Hospital, New Orleans 12, Louisiana.

[2] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.



FIGS. 1–4. Case 1. (Left) Roentgenogram of chest (EPA) revealing small calcified focus in the right third interspace and large calcified mediastinal masses. (Center left) Left anterior oblique view showing more clearly the two large stippled masses, one overlying the trachea, the other overlying the right main stem bronchus. (Center right) Planigram showing erosion of the superior mass into the trachea. (Right) Postoperative roentgenogram revealing removal of masses.

Planigrams were made and revealed that the superior mass was eroding into the trachea (figure 3). Bronchoscopy revealed on the posterior wall of the trachea about 1.5 cm. superior to the carina a small area of thickened mucosa which was ulcerated and reddened. There was no active bleeding from this area at the time of examination. The bronchoscope was then inserted into the right main stem bronchus, where another area of reddening with thickening and ulceration of the mucosa was noted on the posterior wall. The remainder of the tracheobronchial tree was found to be within normal limits. Four weeks later bronchoscopy was repeated. At this time no abnormality was found in the trachea; however, on the right lateral wall of the right main stem bronchus an ulcerated area was noted which was also reddened with mucosal swelling. Acid-fast smears and Papanicalaou stains were done (on the aspirations of both bronchoscopic examinations), but gave negative results. Despite the relative improvement at the time of the second bronchoscopy, it was believed that surgical exploration should be done. This was predicated on the fact that the patient had continued to have hemoptysis and severe chest pains. The patient complained bitterly, and rapidly became addicted to narcotics. The remainder of the studies revealed a tuberculin one plus positive with negative skin reactions to histoplasmin, 1:10,000 and 1:1,000. Four sputum examinations were negative for acid-fast bacilli. A serologic test for syphilis was negative. Peripheral blood count was within normal limits, without abnormality, except for a persistent eosinophilia which varied from 3 to 9 per cent on several examinations. Finally, at the end of June 1948, a right thoracotomy was performed with endotracheal anesthesia, using cyclopropane and ether as the anesthetic. On exposure of the right chest, excellent visualization was obtained. A firm nodular mass was seen on the medial surface of the right upper lobe. The mass and the adjacent lung were firmly adherent to the trachea and superior vena cava. The nodule measured about 4 cm. in diameter. A similar nodular mass was seen at the superior margin of the hilus of the lung, also firmly adherent to the superior vena cava. By careful, sharp, and blunt dissection the superior nodule was dissected from the trachea and blood vessel. This nodule was densely adherent to the lung and, in order to excise it, a crescentic segment of pulmonary tissue was excised. During the process of removal of the mass, a moderate amount of thick, yellowish-white, caseous material escaped into the pleural cavity. The inferior mass was separated from the vena cava with difficulty and was ruptured during its removal; it also contained a similar type of caseous material. The patient convalesced well from this procedure. Summary of the pathologic report revealed that the findings were compatible with an old, primary (Ghon) complex in the lung and lymph nodes, with microscopy revealing caseation necrosis surrounded by a hyalinized connective tissue wall with some chronic pneumonitis and epithelioid tubercles. The patient was discharged three weeks following surgery, at which time he was asymptomatic (figure 4). Follow-up examinations, two and twelve months following surgery, revealed that the patient was getting along well and was without symptoms.

Case 2. A 23-year-old white male was admitted to this hospital on June 1, 1949, complaining of hemoptysis. The patient stated that he had been essentially well until January 1949, at which time he developed a chronic cough productive of small amounts of mucopurulent sputum. No other symptoms were present until two months before admission, at which time the patient noted that he was bringing up small amounts of bright red blood in his sputum. At this time he also noted occasional low-grade fever, mild cervical lymphadenopathy, and recurrent episodes of sore throat. On direct questioning the patient responded with a history of having coughed up small amounts of chalky, gritty material on several occasions.

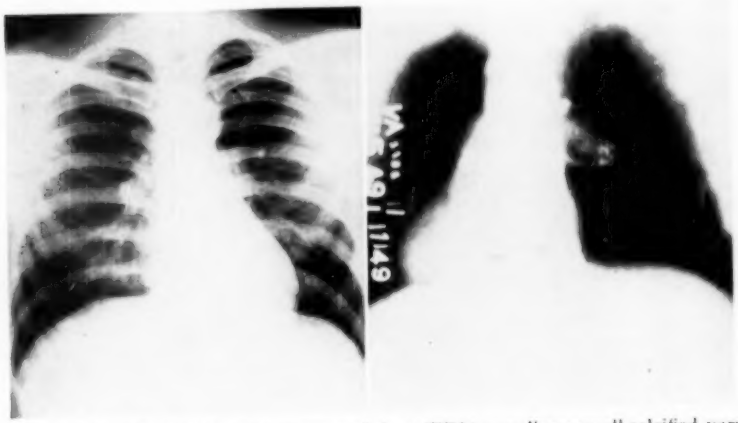
Physical examination revealed a well-developed, well-nourished, white male who did not appear to be ill, and the examination was otherwise unremarkable.

Laboratory findings: The peripheral blood count was within normal limits. Numerous sputum examinations and gastric washings were all negative for acid-fast bacilli. A tuberculin skin test was two plus positive in second strength and skin tests with coccidioidin,

1:100, and histoplasmin, 1:1,000, were negative and one plus, respectively. Sputum culture and guinea pig inoculation yielded no evidence of tubercle bacilli.

The admission roentgenogram of the chest revealed no significant abnormality except for a primary complex with the Ghon tubercle in the peripheral portion of the third interspace on the right. In the right hilum there could be seen two large calcified masses which were assumed to be calcified lymph nodes, part of the primary complex (figure 5). Planigraphic studies with cuts taken through the tracheobronchial tree revealed the largest mass of stippled calcification to be in the right hilum and intimately associated with the middle lobe bronchus (figure 6). The bronchus appeared to be surrounded by part of the calcified node. Another calcified mass was found to lie just above the origin of the right upper lobe bronchus.

Clinical impression at this time was that the calcified masses were eroding into the bronchial tree, causing the hemoptysis and other symptoms. Therefore, bronchoscopy was per-



FIGS. 5-6. Case 2. (Left) Roentgenogram of chest (EPA) revealing a small calcified parenchymal lesion (right third interspace, peripherally) and large calcified hilar masses. (Right) Planigram (A–P) bringing out the contiguity of a calcified mass with the right middle lobe bronchus.

formed and the report revealed that the carina was in the mid-line, but the anterior half was thickened and ulcerated. At the junction of the right main stem bronchus with the trachea, on the lateral wall, another small ulcerated area was seen. No active bleeding was found at either site. The remainder of the bronchial tree was found to be within normal limits.

While under observation in the hospital the patient's symptoms all subsided. Subsequent bronchoscopy revealed that the two ulcers seen in the bronchial tree were both healing. It was believed that the patient's symptoms over the past six to seven months were due to erosion of the bronchial tree by calcified masses. The mass responsible for erosion of the carina could not be demonstrated by roentgenographic examination. The intimate association of the calcified masses with the bronchial tree, as revealed by planigraphy, made the writers feel confident that erosion of the bronchial tree by calcified masses was the cause of the hemoptysis.

COMMENT

As seen in these two cases, the body seems to treat calcified material in the hilar nodes much as it does a foreign body, and there is often constant effort to extrude material

into the bronchial lumen and out into the respiratory tract. It is possible that constant movement of the respiratory tract stimulates the erosive process which occurs.

When the erosive process involves larger bronchi, it may take several courses:

(*1*) Compression of the bronchus with stenosis, e.g., middle-lobe syndrome

(*2*) Perforation of the bronchus with extrusion of the mass into the lumen:

a) There may be repeated extrusion of small, gritty or calcific masses into the lumen.

b) There may be extrusion of large masses into the lumen with atelectasis on an obstructive basis, possibly with secondary suppurative disease, lung abscess, or irreversible bronchiectasis.

If living tubercle bacilli are present, there is always the possibility of a caseous pneumonia or tuberculous endobronchial disease. The same sequence of events occurs much more often in children and in some adults when noncalcified caseous nodes erode into the bronchi. The large scale atelectasis and pneumonitis which often follows this in children has been referred to as epituberculosis and it may be that a small mass strategically extruded can account for this extensive disease which, however, is often rapidly reversible because of the large element of atelectasis present.

Occasionally one sees multiple calcified foci throughout the lung field due to healed miliary tuberculosis or, possibly, histoplasmosis. These cases also present hemoptysis or other evidence of eroding calcified mass, or of broncholithiasis. Usually this is a much milder symptom-complex with involvement of smaller bronchial elements and no atelectasis. A recent patient with long-standing, inactive tuberculosis and roentgenograms characterized by multiple small calcific foci suffered a grand mal seizure followed by persistent productive cough, with sputum markedly positive for acid-fast bacilli. Under observation, the cough subsided and the sputum decreased in amount with disappearance of acid-fast bacilli. It was thought that a calcified focus with viable tubercle bacilli had eroded into a bronchus, causing an endobronchial lesion. No change in the densities on the roentgenogram was noted, and the patient made a complete recovery.

Awareness of the syndrome and application of diagnostic measures in all suggestive situations is important. Such situations would include undiagnosed hemoptysis; atelectasis; bronchial obstruction; wheezing (stone asthma); coughing, often paroxysmal; and persistent mediastinal pain, possibly very severe as in our case. Differentiation of the syndrome from carcinoma of the lung, adenoma, and aspirated foreign body can be difficult.

The first clue to diagnosis is the routine roentgenogram of the chest. Often an overpenetrated film will bring out the hard calcified shadow which is not seen in the softer film. In some cases a careful history with "leading questions" reveals a previous coughing up of calcareous material. Bronchoscopy is of valuable assistance in finding the site of ulceration. It is of value also in removing the foreign material which already may be within the bronchus or for biopsy of the ulcer base to exclude the presence of other possible disease. Examination of biopsy material was not helpful in our cases except in a negative sense. Planigrams can be very helpful, as in the two cases described above, in demonstrating the erosive process. The calcific spicules can often be seen protruding through the bronchial wall. Other routine diagnostic measures, such as sputum examinations for tubercle bacilli, are essential for proper evaluation.

Two different types of management were used in the two cases. In one case, conservative observation only was used and will be maintained. In the other patient, operative intervention was used when symptoms became severe enough because of recurrent hemorrhage and constant pain which made the patient an invalid and narcotic addict. General indications for surgery would be severe, recurrent hemorrhage; progressive bronchial

stenosis, with or without pulmonary disease secondary to obstruction; severe pain or any other situation where the possible consequences of the erosion seem to threaten the general welfare of the patient. Bronchoscopy with aspiration of foreign body could be used if calcified material eroded into the bronchus and lodged there. Otherwise, bronchoscopy is of value in helping to exclude the presence of other conditions which enter into the differential diagnosis. In those instances where symptoms resulted from erosion by miliary or minute areas of calcification throughout the lung field, conservative management would be the only method available. It is interesting to find very few references in the American literature to the use of thoracotomy for removal of hilar nodes which are eroding into the bronchus. A good deal has been written about broncholithiasis and the use of the bronchoscope for removal of the calcified foreign bodies. Also, much has been written about lobectomy as treatment for the suppurative process distal to bronchial obstruction. Most cases of thoracotomy with removal of nodes have been carried out in cases of tuberculous mediastinal lymphadenitis because of the erroneous diagnosis of bronchogenic carcinoma with superior vena caval syndrome.

Erosion of calcified hilar lymph nodes into the bronchial lumen is not an unusual condition. Diagnosis should be made preferably before the eroding mass causes irreversible damage by obstruction of the bronchial lumen. Although conservative management is considered best for the usual eroding nodes, it is believed that thoracotomy has its place in the management of cases with severe pain or in other cases that threaten the patient with possible severe complications. Bronchoscopy is of importance mostly for diagnosis, but also for the treatment of broncholithiasis, the condition which exists when calcified matter is lodged in the bronchial lumen.

SUMMARY

Two cases have been reported representing two different aspects of the problem of eroding calcified hilar nodes. The different approaches to management of such problems have been discussed as have various aspects of pathogenesis, diagnosis, and management.

SUMARIO

Erosión de Ganglios Linfáticos Mediastínicos Calcificados

Comunícanse dos casos que representan dos fases distintas del problema de la erosión de los ganglios calcificados del hilio. Discútense las diversas formas de abordar el tratamiento de dichos problemas, e igualmente varios aspectos de la patogenia, diagnóstico y asistencia.

ARTIFICIAL PNEUMOPERITONEUM COMPLICATED BY PREGNANCY[1]

STANLEY H. SAHN AND HYMAN E. BASS

(Received for publication March 29, 1950)

The use of artificial pneumothorax in the treatment of tuberculosis associated with pregnancy is well known and the management of this type of case presents few difficulties. In more recent years, artificial pneumoperitoneum has received increasing attention in the treatment of pulmonary tuberculosis (1–4). It is to be expected that an increasing number of patients receiving pneumoperitoneum therapy may become pregnant during the course of their treatment and will pose a problem in management. The following report illustrates some of the considerations involved in this type of case.

CASE REPORT

The patient, B. A., was a 28-year-old Negro female who dated the onset of her present illness in March 1947. There was no familial history of tuberculosis; the only known contact was with a neighbor who had active pulmonary tuberculosis. The onset was insidious, with cough for which she received symptomatic treatment. A few weeks later she developed high fever and was treated with penicillin. The diagnosis of pulmonary tuberculosis was established in May 1947 and the patient was hospitalized but left against advice after ten days. A return of fever and chills in August caused her to seek hospitalization again and on September 9, 1947 she was admitted to a tuberculosis sanatorium.

On admission she was found to be undernourished and appeared chronically ill. She complained of right chest pain, dyspnea, and cough productive of approximately 180 cc. of bloodless sputum. Dullness and bronchovesicular breathing over the right lower chest were noted, with crepitant and wheezing rales in the same area. Blood pressure was 100 systolic and 65 diastolic in mm. of mercury. Temperature was slightly elevated. Laryngoscopy on November 15, 1947 revealed tuberculous granulations in the posterior commissure.

A roentgenogram of the chest at the time of admission disclosed a giant cavity (4.5 cm. by 4.0 cm.) with a fluid level in the right lower lung field partially obscured by the right cardiac border. There were exudative infiltrations in the adjacent lung and productive lesions in the first two anterior interspaces while the contralateral lung was clear. Sputum concentrates were highly positive for acid-fast bacilli. The erythrocyte sedimentation rate was 27 mm. in one hour. A blood count showed the following: concentration of hemoglobin, 79 per cent; erythrocytes and total leukocytes, 4,100,000 and 6,000 per cu. mm., respectively; segmented neutrophils, 38 per cent; nonsegmented neutrophils, 31 per cent; lymphocytes, 20 per cent; monocytes, 9 per cent; eosinophils, 2 per cent. The urine was essentially negative. A serologic test for syphilis (Mazzini) was negative.

The patient was placed on strict bed rest. Because of the location of the cavity in the lower lung field, an artificial pneumoperitoneum was induced successfully on October 10, 1947. Sputum continued consistently positive for tubercle bacilli until February 1948. The cavity, however, gradually decreased in size but other areas of rarefaction persisted. A course of streptomycin (totaling 27 gm.) was administered for the tuberculous laryngitis from November 14, 1947 to December 21, 1947. Laryngeal examinations, January 20 and February 20, 1948, revealed complete clearing of the granulations. The low-grade fever subsided while the patient received streptomycin; no subsequent elevations occurred. A bronchoscopy was performed January 10, 1948 and revealed mild inflammatory reaction in the bronchi to both lungs, impaired drainage particularly in the right lower lobe bronchus,

[1] From the Department of Thoracic Diseases, Beth-El Hospital, Brooklyn, New York.

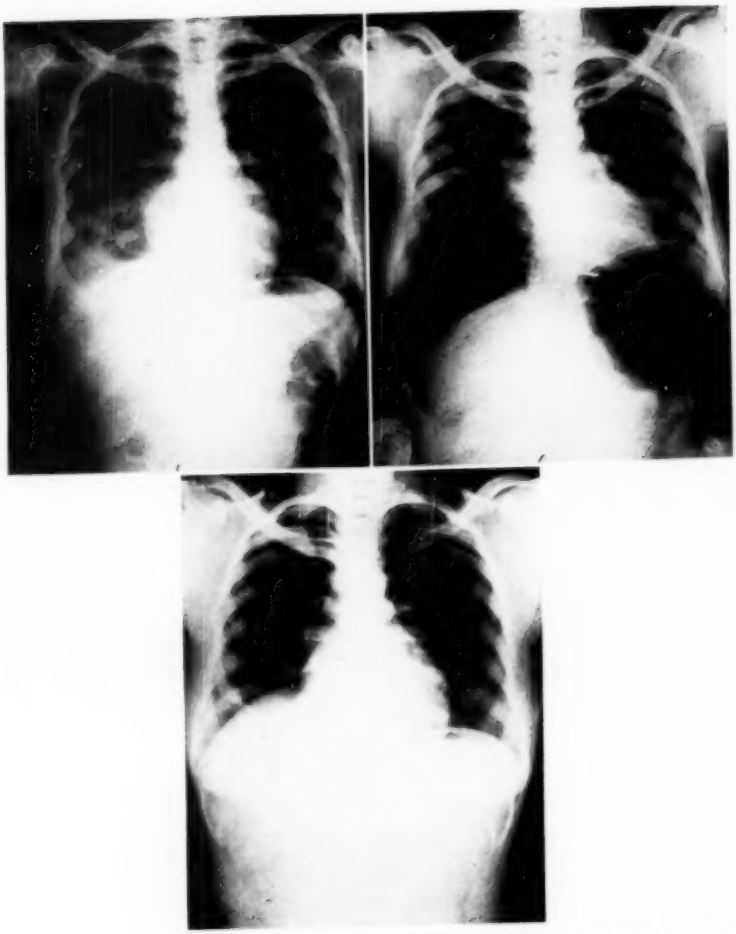


FIG. 1. (Upper left) Admission roentgenogram, October 10, 1949, showed a large tuberculous cavity with a fluid level in the right lower lung field adjacent to the cardiac border.

FIG. 2. (Upper right) Roentgenogram showing pneumoperitoneum and high elevation of right diaphragm due to phrenic crush. The cavity in the right lung is no longer visible.

FIG. 3. (Bottom) Roentgenogram taken after termination of pregnancy. Artificial pneumoperitoneum is no longer present. No cavity is seen in the right lung. The right leaf of the diaphragm is elevated.

and complete block of the right middle lobe bronchus by accumulated mucous secretions one-fourth of an inch from the orifice.

The patient demonstrated clinical and roentgenographic improvement. The erythrocyte sedimentation rate dropped to 16 mm. in one hour on February 4, 1948. Sputum examina-

tions were chiefly negative for tubercle bacilli from February 3, 1948 on, though gastric cultures were uniformly positive. A right phrenic crush was done on March 1, 1948 to supplement the pneumoperitoneum; there was resultant paralysis of the right leaf of the diaphragm, which reached the level of the fifth posterior rib, and roentgenographic obliteration of the cavity. On March 9, 1948 the patient left the hospital against advice.

Pneumoperitoneum refills were continued on an ambulatory status while the patient carried on light duties as a housewife. Intervals between refills were gradually lengthened from one to two weeks with an average of 1,200 cc. of air at each injection. Sputum concentrates at almost monthly intervals were consistently negative for tubercle bacilli, as were three sputum cultures. Serial roentgenograms revealed no change. Cavitation was not demonstrable in postero-anterior or lateral projections. Erythrocyte sedimentation rates ranged from 43 mm. to 56 mm. in one hour. There was a loss of four pounds following discharge from the sanatorium. In the early part of December 1948, the patient reported that her menstrual period was overdue. She was found to be pregnant and registered with the prenatal clinic of the Beth-El Hospital. Injections of air were continued at about two-week intervals with amounts varying from 700 cc. to 1,300 cc. No difficulty was encountered until April 14, 1949 (twenty-fifth week of pregnancy) when the pneumoperitoneum was discontinued because of increasing discomfort. The patient complained of excessive cough and marked pressure sensations beneath the diaphragm and in the pelvis immediately following the instillation of air. It was also noted that air appeared to absorb more rapidly than before pregnancy and the initial readings became considerably lower. As the fundus rose in the abdomen the site of injection was changed from para-umbilical to subcostal but even at the higher level the needle was felt to rub the fundus when the latter lay only three fingers above the umbilicus.

The prenatal course was relatively uneventful. On July 7, 1949, in her thirty-seventh week of pregnancy, the patient was admitted to the Beth-El Hospital on the obstetrical service for elective cesarean section because of cephalo-pelvic disproportion. Pelvimetry disclosed a platypelloid-gynecoid pelvis. Past history revealed that there had been three previous pregnancies. The first two ended in prolonged labor of three and one-half days each; the second pregnancy resulted in death of the infant from cerebral injury. The third pregnancy terminated in spontaneous abortion in the second month. On the eleventh hospital day, low cervical two-flap cesarean section was carried out under fractional spinal anesthesia. A viable male infant weighing 1.98 kg. was delivered and a Pomeroy sterilization performed. The postoperative course was without incident. Sputum and gastric culture while in the hospital proved negative for tubercle bacilli. A chest film on July 16, 1949, two days before operation, was reported to show " . . . no evidence of recent or active parenchymal infiltration of pleural involvement." The patient was discharged on the twenty-third day.

In the six-month period since delivery, there has been no evidence of reactivation of the pulmonary disease. Pneumoperitoneum was not reinstituted. The patient has been asymptomatic and has gained weight while carrying out her duties at home. The sedimentation rate has fallen to 19 mm. in one hour. Repeated sputum concentrates have been negative. Roentgenograms on August 25, 1949 and December 27, 1949 in postero-anterior and lateral views disclose only a small productive nodule at the right base. The diaphragm remains considerably elevated as the result of the right phrenic crush on March 1, 1948. Although fluoroscopy immediately post partum disclosed little motion of the right diaphragm, examination six months later revealed increased motion in the elevated right leaf.

COMMENT

The use of artificial pneumoperitoneum immediately following pregnancy has been described. In such instances, the purpose of therapy has been to maintain the elevation of the diaphragm which had existed during pregnancy. It has been shown that motion of the

diaphragm is restricted in the ninth month of pregnancy and returns immediately after delivery in 85 per cent of cases, subjecting the tuberculous lung to respiratory strain (6).

On the other hand, the management of the patient who becomes pregnant while receiving artificial pneumoperitoneum has received scant attention in the literature. Banyai (5) has mentioned only one case of pregnancy occurring during the course of an artificial pneumoperitoneum. He stated that refills should be given with the usual amounts of air. The pneumoperitoneum is gradually discontinued during the eighth month when the uterus maintains the diaphragm at a high level. He recommends immediate re-establishment of the pneumoperitoneum post partum.

The case presented in this report received pneumoperitoneum refills until the twenty-fifth week when technical difficulties were encountered. The decision against reinstitution of pneumoperitoneum immediately following delivery was influenced by the presence of a high diaphragm due to residual phrenic paralysis. It was believed that this was sufficient to maintain relaxation of the diseased right lung. Cesarean section did not influence this decision. It has been pointed out (5) that pneumoperitoneum may be instituted directly after completion of cesarean section.

SUMMARY

A case of artificial pneumoperitoneum complicated by pregnancy has been described. Refills were continued until the twenty-fifth week of the pregnancy. The presence of residual phrenic paralysis made post-partum reinduction of artificial pneumoperitoneum unnecessary.

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Editorial

The Hemagglutination Test in Tuberculosis

The unequivocal diagnosis of an infectious disease is most effectively established by the isolation and identification of the infecting organism. In many infections, however, it is so difficult to isolate or identify the parasite that one must rely upon serologic methods. This is often the case in filtrable virus infections. Infection or disease due to tubercle bacilli presents a somewhat special case. Tuberculosis in the vast majority of affected human beings takes the form of a subacute or chronic disease, exhibiting temporary remissions and exacerbations and lasting long enough to permit the development of specific circulating antibodies, before the final outcome of the host-parasite relationship is achieved.

The isolation and identification of tubercle bacilli from the affected host are well-established procedures giving certainty to the diagnosis of active tuberculous disease regardless of the other presumptive clinical or laboratory data. In contrast, the tuberculin test, so useful in epidemiologic studies, is of no value in establishing the diagnosis of disease, although a negative reaction to tuberculin is statistically strong evidence against infection or disease by tubercle bacilli except under certain relatively rare conditions. It gives no useful information, however, as to whether the tuberculin-sensitive individual has active, progressive disease or has merely been subjected, within a long interval of time, to a relatively innocuous infection with tubercle bacilli. It is not necessary to emphasize further the difference between infection and progressive disease. The importance of this distinction has long been recognized. Indeed, before the more effective present methods of isolating tubercle bacilli were introduced, the search was intense for a serologic test which would identify the diseased among the great mass of infected individuals. Bordet and Gengou in 1903 demonstrated the specific fixation of complement by tuberculous serum in the presence of whole tubercle bacilli as antigen. In 1906 Wassermann with Bruck began his work with a complement fixation test, using Old Tuberculin as the antigen, before he turned to the adaptation of the test to the diagnosis of syphilis. Since that period Petroff, Wadsworth, and the Maltaners in this country and Witebsky in Europe, among many other investigators, have studied the usefulness of complement fixation methods for the detection of specific antibodies in the sera of tuberculous individuals.

The consensus of opinion of the value of complement fixation procedures in the diagnosis of tuberculosis has been unfavorable during the past few decades. Wadsworth's hope that further standardization of the antigens, and possibly some preliminary treatment of the patient's serum to eliminate false positive reactions, has not been realized. Nevertheless, none of the many other serologic

reactions, which have shown early promise of possible usefulness as supplementary aids to the clinical and bacteriologic diagnosis of tuberculosis, have been as close to success as the complement fixation reaction. The complaint, if it can be called such, of the serologist has been that the amount of specific serum antibody is too small in the tuberculous patient to permit the available serologic tests to be useful clinically. It is interesting to note in passing that this fact stands in paradox to the well-known enhancing effect which tubercle bacilli have as adjuvants on heterologous antigens.

In 1948 a hemagglutination reaction was described[1] for the detection of small amounts of antibody against what is probably one or more polysaccharide antigens (or haptenes) of mammalian-strain tubercle bacilli. By means of this reaction, antibody was readily detected in the sera of patients with active tuberculosis, and preliminary studies showed that the reaction was highly specific.[2] The significant condition, it seems, which endows this hemagglutination reaction with such high specificity is the fact that only a small proportion of the several antigens of the tubercle bacillus is adsorbed firmly onto the red cells. The phenomenon of selective adsorption of this as yet ill-defined antigen or antigens is in itself a physicochemical purification which appears to eliminate those components of the tubercle bacillus which are capable of giving false positive serologic reactions.

The relatively greater sensitivity of agglutination reactions over precipitin reactions for the detection of small amounts of antibody is well known. Thus, the hemagglutination reaction is preferred to precipitin reactions between carbohydrate fractions of tubercle bacilli and serum antibodies. It seems appropriate to mention here the interesting fact that the addition of complement to the hemagglutination system transforms the reaction from one of specific agglutination of red cells to one of hemolysis. Preliminary observations with human sera indicate that this hemolytic modification of the hemagglutination test may have some advantages over the original test.

It is important to consider here the general problem of the possible limits of usefulness of a test for the presence in human sera of specific antibodies against the antigen(s) of tubercle bacilli.

It is a well-established immunologic fact that for any particular antigen some individuals in a large population will fail to respond by the production of specific antibodies. In other words, no serologic test for infectious disease is diagnostically perfect in the sense that every individual will respond by the production of specific antibody. Therefore, it is conceded *a priori* that no serologic test for tuberculosis which measures gamma-globulin antibodies can be expected to give 100 per cent positive results in patients with active disease.

[1] Middlebrook, G., and Dubos, R., J. Exper. Med., 1948, *88*, 521.

[2] The specificity of the reaction depends, above all else, upon the use of the proper antigen for sensitizing the red cells. Early in the clinical investigation of the test, an extract of tubercle bacilli prepared with the use of trypsin gave many false positive reactions. More recently, both in this country and in France, carefully prepared Old Tuberculin preparations, showing very high specificity, have been used extensively and appear to be particularly suitable for sensitizing erythrocytes for the hemagglutination test.

It is also well known that specific antibodies are often absent from the serum of individuals with severe infectious diseases; indeed, specific and nonspecific immunologic reactions are often depressed in very sick individuals. Consequently, it is reasonable to expect that many very toxic patients with tuberculosis will fail to have demonstrable circulating antibodies against tubercle bacillus antigens.

The material which sensitizes red cells in the hemagglutination reaction appears in culture filtrates of tubercle bacilli only in association with lysis or "breakdown" of the bacilli. It seems likely, therefore, that the rate of lysis of the bacilli in the diseased host will be a more important variable than will the actual numbers of living or multiplying bacilli in determining the rate and extent of formation of antibodies. The conditions which determine the rate of lysis of tubercle bacilli *in vivo* are not known. Nevertheless, it is reasonable to assume that the release of the antigen(s) which stimulates the production of the antibodies responsible for the hemagglutination reaction ceases soon after the bacilli stop multiplying and spreading.

It is well established that reinjection of an antigen to which the host has previously responded by antibody production stimulates a prompt, accelerated release of specific circulating antibodies. This is called the "anamnestic" response. It may occur within three or four days. Not only does this phenomenon explain the already observed effect of tuberculin testing on the hemagglutination titer of human sera,[3] but it suggests that the hemagglutination test may be useful in detecting reactivations of tuberculous disease even before other evidence such as a roentgenographic change is manifest.

Finally, the question naturally arises whether or not the hemagglutination test has any bearing on acquired resistance or immunity to tuberculosis. The mechanisms of acquired resistance to tuberculosis are as yet undefined. Indeed, there is no convincing evidence that circulating antibodies against components of tubercle bacilli have any necessary bearing on immunity in this disease. Thus, no positive evidence is at hand to suggest that the antibodies measured in the hemagglutination test or its modifications are directly related to the mechanism of protection. Indeed, it seems reasonable at the present time to assume that these particular antibodies have no necessary relation to resistance.

In view of these theoretical aspects of antibody formation in tuberculosis, one may be permitted to suggest the following possible limits of usefulness of the hemagglutination test for tuberculosis:

1) The high degree of specificity of the reaction, when a reliable antigen is used and after experience has been obtained in the performance of the test, suggests that a positive reaction at 1:8 or higher dilution of serum is presumptive evidence of disease due to tubercle bacilli or to a *Mycobacterium* very closely related in antigenic structure.[4]

[3] Smith, D. T., and Scott, N. B., Am. Rev. Tuberc., 1950, *62*, 121.

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Scott, N. B., and Smith, D. T., J. Lab. & Clin. Med., 1950, *35*, 303.
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2) A certain percentage of individuals with clinically active tuberculous disease will fail to give a positive hemagglutination reaction. Some of these individuals will fail to give a positive reaction because of the severity of their illness; and others, simply because they do not respond with antibody production against the antigen which is involved in the test.

3) The test will become negative after a period of freedom from spreading disease. This may occur even when viable tubercle bacilli are still present in the tissues of the infected host, and may serve as a source of bacilli for reactivation of the disease.

4) Reactivation of the disease may be detectable by the hemagglutination test before other evidence of such is obtainable by present diagnostic methods.

5) No conclusions are justified concerning the state of resistance of the individual on the basis of the results of the hemagglutination test; nor can the titer of reaction in the test be a measure of the degree of "activity" of the disease.

6) As is the case with any other laboratory procedure, undue stress on the hemagglutination test in contrast to a comprehensive clinical, bacteriologic, and roentgenographic evaluation of the patient will constitute bad medical practice.

GARDNER MIDDLEBROOK

Letters to the Editors

TRANSMISSION OF STREPTOMYCIN-RESISTANT TUBERCLE BACILLI

To the Editors of the American Review of Tuberculosis:

The following case report constitutes an example of the potentially serious problem of transmission of streptomycin-resistant tubercle bacilli:

A 24-year-old white student nurse had a positive tuberculin skin reaction and a negative roentgenogram of the chest on admission to nursing school in 1944. In 1946 she was assigned to the tuberculosis service for two months. Among the patients on that service were six whose sputum cultures yielded strains of tubercle bacilli highly resistant to streptomycin (> 1,000 γ per ml.). Semiannual roentgenograms of the chest remained negative from 1944 to 1949, at which time a minimal tuberculous infiltrate was noted. Tubercle bacilli were cultured from her gastric aspirate on three separate occasions, and all three strains were found to be highly resistant to streptomycin in concentrations as high as 1,000 γ per ml. She had never been treated with streptomycin.

Case reports of tuberculous infection by streptomycin-resistant organisms are as yet quite rare. In each instance it seems impossible to state with finality whether the tubercle bacilli were natively resistant or had been transmitted from a patient whose organisms had become resistant as a result of streptomycin treatment. It is clear that in any strain of tubercle bacilli highly sensitive to streptomycin one may expect to find a few cells moderately resistant to this drug. The large number of sensitivity tests done prior to administration of streptomycin indicate, however, that significant resistance to streptomycin in the untreated must be extremely rare. The rarity of this occurrence, the high degree of resistance, and the known contacts of this nurse lead us to assume that her infection was contracted from a resistant source. That streptomycin-resistant organisms might be transmitted from treated to untreated individuals has not been altogether unexpected. As more patients receive this drug, it is conceivable that the frequency of this occurrence will increase, posing a serious therapeutic problem.

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BOOKS

E. T. Bernard, B. Kreis, and A. Lotte: *Tuberculosis Treated with Streptomycin (Tuberculoses Traitées par la Streptomycine). Pp. 172 with illustrations, L'Expension Scientific Francaise, 1949, Price 800 francs.*

The effectiveness of streptomycin in the treatment of various forms of diseases due to the tubercle bacillus depends largely upon the type and the localization of the pathologic process. The most striking results are obtained in treating tuberculous meningitis and miliary tuberculosis, provided that the disease is recognized early enough. The art of early diagnosis of tuberculous meningitis before the outbreak of the classical neurologic symptoms is, as described in the first chapter of this book, the key to successful treatment with streptomycin. And it seems that not everywhere is one familiar with the first signs and symptoms of this disease. This fact perhaps explains the better results reported from France and England, and from one group in the United States, in the streptomycin treatment of tuberculous meningitis in adults, compared with those generally reported in this country. (For results obtained with children see: R. Debré, S. Thiéffry, et H. E. Brissaud: *La Streptomycine Appliquée au Traitement de la Méningite Tuberculeuse et de la Tuberculose Miliaire*, Masson et Cie, Paris, 1948).

According to the authors' statistics, twenty-two of one hundred adult patients with tuberculous meningitis, diagnosed either bacteriologically or by post-mortem findings, are still alive. The majority of those survived the beginning of the treatment for two years. Of the seventy-eight patients who died, eighteen died within five days after admittance to the clinic. They all arrived in deep coma, and no response to the administration of streptomycin was observed. Forty-nine patients died after a first period of remission between the sixth and one hundred and eightieth days of treatment. Only eleven deaths occurred at a later time. Thirty-six of all one hundred cases developed meningitis as a complication of miliary tuberculosis of the lung. Systematic examination of the spinal fluid helped to recognize this complication at an early pre-clinical state. The same is true for the detection of relapses during the course of treatment. The remission can be either incomplete, leading to chronic meningitis with relapses during treatment, or complete with disappearance of all symptoms. Thirty-two of the patients reached this condition and treatment was discontinued; fifteen of them had relapses. In these patients the number of relapses is inversely related to the number of weeks of treatment; the earlier the treatment was discontinued, the greater was the number of relapses. From the beginning, 0.1 gm. of streptomycin was injected daily intrathecally for ten to fifteen days. Intramuscular daily injections of 1.0 to 1.5 gm. were given over an average period of seven months to the patients who were ultimately cured.

In the second part, the treatment of one hundred and fourteen cases of miliary tuberculosis of the lungs is described. Of the forty-nine fatal cases, thirty-

seven had complicating tuberculous meningitis. Thus, this combination seemed to be the most severe form of tuberculosis. The average treatment lasted for three months.

In the remaining chapters, results in the streptomycin treatment of other types of pulmonary tuberculosis in combination with pneumothorax and surgical intervention are described, as well as of bronchial, laryngeal, pharyngeal, and bone tuberculosis. As the results are comparable to those reported in this country, no further details need to be given.

The value of this and Debré's book lies in the careful analysis and description of the course of tuberculous meningitis treated with streptomycin. The evaluation of the methods of early diagnosis of meningitis and of the occurrence of relapses during treatment is of special interest.

EMANUEL SUTER

DONATO G. ALARCON: *Surgical Extrapleural Pneumothorax. Pp. xi-298 with illustrations, Imprenta Universitaria, Mexico, 1948.*

The author considers extrapleural pneumothorax to be a desirable form of semipermanent collapse in which complications are infrequent and which does not require the patient to be a slave to a therapeutic regimen for many years. Its advantages over thoracoplasty are that it leaves no deformities and is reversible.

Throughout the text one is cognizant of the fact that Doctor Alarcon is keenly aware that the procedure has met with disfavor by many phthisiologists. It is the author's firm belief that the unfavorable criticism is not justified. He believes that his meticulous selection of cases, his operative procedures, and careful postoperative care explain the differences between his success and the failure of others. He believes that most men have not had a large enough series to adequately judge the procedure. Commenting on this point, Doctor Dolley, in a preface to the book, states that this very important operative procedure has received distressingly little consideration in the United States.

Beginning with a short historic review of the development of the procedure, the author continues with the indications for therapy. It is his belief that with the proper selection of cases one may expect success in ninety per cent of them. In his discussion of the operative procedure, he lays much stress on the choice of anesthesia, the pre- and post-operative care of the patient.

The operation itself is amply demonstrated by photographs and drawings, and his handling of complications are discussed in great detail. Oil is substituted for air in those instances where the patient cannot obtain refills from his physician or where a permanent collapse is desirable.

An interesting feature of the book is the reproduction of more than one hundred roentgenographic illustrations, with accompanying drawings amplifying the roentgenograms.

The book is an excellent treatise on this subject. In this period of increasing use of resectional surgery, however, it will probably not receive much attention in this country.

OSCAR AUERBACH

HANS KRAUS,: *Principles and Practice of Therapeutic Exercises, Pp. 309, Charles C Thomas, Springfield, Illinois, 1949, Price $6.50.*

The author attempts to organize and systematize exercise therapy. The book is divided into three parts. The first discusses the general principles of exercise therapy, and the second and third indicate exercises directed towards specific parts of the body and general exercise.

The orientation is basically clinical and although a few physiologic facts are given this aspect of exercise is not exploited. One regrets that exercise therapy is not truly an outgrowth of what has been learned by the techniques of nerve muscle physiology and the studies of the Fatigue Laboratory. It could be claimed, rightfully, that such material is not within the scope of this book. More than likely, however, the application of what has been learned from the isolated nerve muscle preparation to the intact human is an enormous task which must some day be worked out. The subjective nature of symptoms and signs such as pain, weakness, spasm, and shortening make accurate objective evaluation impossible. The author clearly makes the point that the use of complicated gadgets designed to measure muscle strength does not make the observations objective. All such measurements indicate the strength of the muscle plus or minus the motivation of the individual. Witness hysterical palsy and the "superhuman" strength of the manic. Accurate data on the range of variation in the signs and symptoms of muscle disorder is lacking. Evaluation of pain depends upon the patient's description of a subjective experience. Separation of voluntary from involuntary spasm is frequently difficult. An ergometer which will tell the maximum strength of a given muscle has never been designed. The author, through his skill and experience, designates clinical criteria and "rules of thumb" which are helpful to the therapist.

Evaluation of the results of exercise therapy is not considered in this book. One wonders whether accomplishments are always the result of the exercise alone. The simple psychotherapeutic techniques of interest, sympathy, encouragement, and distraction are active. While our knowledge is in its present stage, possibly we should cease evaluating results of therapy in terms of how many degrees a joint can be moved or how much resistance can be overcome. Accomplishment of a given task is the desired end result as has been demonstrated by those who work in rehabilitation. Doctor Kraus has not lost sight of this objective in describing his exercises. For the patient's sake we must accept results without *post hoc* reasoning. At best, therapeutic exercises, when properly applied, can make the difference between a bedridden invalid and a productive member of society, as has been shown repeatedly. Whether the technique involves psychotherapy or not is irrelevant since the term implies only that the exercises are therapeutic and does not indicate how the therapeutic effect is brought about. The very least exercises can provide is a harmless placebo free of the danger of drug idiosyncrasy, and free of the insult of a sugar pill.

Among the detailed exercises described, breathing exercises have a prominent place. It is probable that their usefulness has not been fully exploited.

GEORGE A. WOLF, JR.

THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

Edited by LAWRENCE B. HOBSON

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CLINICAL STUDIES, TUBERCULOSIS

Congenital Aspiration Tuberculosis.—In the last seventy years about 115 cases of proved congenital tuberculosis have been described. The bacilli usually entered the fetus through the umbilical vein and the primary focus developed in the liver. Only 7 cases have been reported in which congenital tuberculosis was limited entirely to the lungs, suggesting an aspiration type of infection. An additional case is described in a male baby born five weeks prematurely. He was the mother's first child and her health had been good except for unexplained fever at the beginning and end of pregnancy. The baby weighed just under six pounds and appeared normal; the placenta showed no gross abnormality. The baby was taken home at the age of 11 days, but there suffered gastrointestinal disturbances and progressive dyspnea. His rectal temperature rose to 101°F. and he was returned to the hospital a week after departure. Fine crepitant rales were heard over the lungs; extensive miliary infiltrations were disseminated throughout both lung fields, being most prominent in the right lower lobe. Death occurred at the age of 22 days. At autopsy both lungs were studded with small, grayish-white nodules measuring 1 to 3 mm. The nodules were composed of necrotic hyaline material containing many acid-fast bacilli. There was no tubercle formation. The lesions appeared to be largely intra-alveolar, suggesting an aspirated infection. Cultures and guinea pig inoculations were positive for *M. tuberculosis*. There were no enlarged lymph nodes and the remaining organs showed no miliary spread. The mother gave no evidence of extragenital tuberculosis, but postpartum cultures from her cervix were positive for *M. tuberculosis;* the cervix contained epithelioid tubercles. All other postnatal contacts in the nursery and at home were free of tuberculosis. It would appear that fetal aspiration of heavily infected amniotic fluid provided a massive and rapidly fatal inoculation.—*Congenital pulmonary aspiration-tuberculosis. Report of a case, A. J. Hertzog, S. Chapman, & J. Herring, Am. J. Clin. Path., December 1949, 18: 1139.—(J. S. Woolley)*

Primary Complex of Skin.—A 63-year-old farmer experienced an injury to his big toe while walking barefooted. Four months later a large ulceration had developed at that place; there were papules on the leg and swollen lymph nodes on the thigh. On the basis of histologic and bacteriologic examination, the diagnosis of a tuberculous primary complex of the skin was made. This was considered to be a reinfection, since roentgenologic examination of the chest revealed the calcified remnants of an old primary focus. A Mantoux test was positive. The skin changes on the leg were considered to be papular tuberculoderma not observed before in a primary complex. The lesions healed completely.—*Beitrag zur Klinik und Pathogenese des tuberculösen Primärkomplexes an der Haut, A. Musger, Wien. klin. Wchnschr., December 16, 1949, 61: 905.—(G. C. Leiner)*

Collapsed Lung in Primary Tuberculosis.—In a series of 821 children showing positive tuberculin tests, 39 (4.7 per cent) had collapse of one or more pulmonary lobes or of a segment. The incidence was highest in the youngest age groups. There was a history of contact with an open case of tuberculosis in

30. Only 10 were asymptomatic; the most frequent symptoms being cough in 25. Eleven had recent febrile episodes and many had other constitutional symptoms. Altogether, 35 required sanatorium care. In 3 cases, more than one lobe was involved. The right upper and middle lobes were each involved in 14 cases, left upper in 7, right lower in 5, and left lower in 3. Of 32 cases followed for two to seventeen years, 28 showed no residual collapse. In 4, the lesions persisted. In more than half, re-expansion occurred within a year. The longest period of re-expansion was three years. For more complete evidence of re-expansion and absence of residua, bronchography is indicated. Unfortunately, because of the war years, this could be performed in only 13 cases and showed bronchiectasis or persistent collapse in only 3. It is very possible that mild bronchiectasis might have been demonstrated in some of the other cases. It is probable that some cases of bronchiectasis seen in later life have their origins in pulmonary collapse in the course of primary tuberculosis.—*Collapse of the lung associated with primary tuberculous lesions, A. M. MacPherson & V. U. Lutwyche, Thorax, March, 1950, 5: 1.*—(*A. G. Cohen*)

Bronchiectasis after Bronchostenosis.—In a series of 400 cases of primary tuberculous lung lesions in children, 77 (19 per cent) showed collapse of a segment, lobe, or lung. Bronchography was performed in 37 of these cases and showed bronchiectasis in 34. In 12 others, the plain films also showed evidence of bronchiectasis, making a total incidence of at least 60 per cent. The cases were followed for as long as seven years. The right lung was involved more often than the left and the upper lobes more often than the lower. The bronchiectasis often was asymptomatic. The bronchial distension was due to retained secretion, tuberculous caseation or secondary infection, the latter being most important. Studies of intrapleural pressure under general anesthesia revealed no significant alterations. To prevent permanent bronchiectasis, it is important to treat the secondary infection vigorously until the collapsed portion re-aerates.—*Bronchiectasis in primary tuberculous lesions associated with segmental collapse, J. C. Roberts & L. G. Blair, Lancet, March 4, 1950, 1: 386.*—(*A. G. Cohen*)

Bronchial Occlusion and Collapse Therapy.—Bronchial occlusion, either healed or active, has a deleterious effect upon the tuberculous lung. In collapse therapy it is an unfortunate complication. The bronchi are often involved in exudative pulmonary tuberculosis and, when pneumothorax is given, further narrowing may cause complete collapse of one or more lobes. It is frequently observed after pneumonolysis. This is a dangerous situation in which empyema and spread are frequent complications. Thus, in 50 cases of empyema, 43 could be traced back to an "opaque" lobe. If lobar collapse develops, an attempt should be made to re-aerate the lobe by varying the size of refills, positioning of the patient during sleep, and altering the height of the diaphragm. Should these measures prove unsuccessful, the pneumothorax should be abandoned. Streptomycin and bed rest before the pneumothorax induction may prevent this development by causing subsidence of the bronchial disease. In distension cavities there are two etiological factors, an area of necrotic lung and a check-valve mechanism. Collapse therapy may accentuate or relieve this situation; the outcome can only be determined by trial and error. It is believed that the chief factor in accomplishing cavity closure is the maintainence of an open bronchus. Sometimes, the addition of phrenic paralysis to pneumoperitoneum may alter the position of the bronchus and cause it to reopen. In Monaldi drainage, cavity closure is accomplished first, then bronchial healing; otherwise, a check-valve mechanism will reopen the cavity. In cases of thoracoplasty following Monaldi drainage, studies made with a catheter in the cavity showed that cavity closure requires open bronchi.—*Collapse therapy and the bronchus, L. E. Houghton, Tubercle, March, 1950, 31: 51.*—(*A. G. Cohen*)

Lung Puncture in Artificial Pneumothorax.—A series of 38 cases was reported in 1947 to demonstrate that puncture of the lung is practically unavoidable in inducing pneumothorax despite technical refinements including the short, blunt needle. In 17 more recent cases, the spontaneous pneumothorax was of small volume. Prevention of serious accidents depends upon avoiding or minimizing the extent of the pulmonary tears. In order to avoid further puncture of the lung immediate introduction of 150 to 200 cc. of air is advocated. Symptoms may be most unpleasant, especially in cases of bilateral pneumothorax, if the functional capacity of the contralateral lung is greatly reduced. The most serious hazard is the possibility of a cerebral air embolism when a vein is involved.—*La punción del pulmón es inevitable en la instalación del neumotórax artificial, A. Vadone, L. M. Dotti, & E. S. Dotti, Rev. argent. de tuberc., 1949, 13: 43.*—(*A. A. Moll*)

Tuberculosis of Ribs.—There are 3 types of tuberculous lesions of the ribs as seen on the roentgenogram: (*1*) expanding, cyst-like lesion entirely within the rib, (*2*) destruction at the lower border of the rib, and (*3*) complete destruction of the rib resembling metastatic malignancy. Complications such as pathological fractures, tuberculosis of other bones, and occasional tuberculous mediastinal lymphadenitis may occur.—*Tuberculosis of the ribs, S. A. Leader, Am. J. Roentgenol., March, 1950, 63: 354.*—(*T. H. Noehren*)

Tuberculous Broncho-arterial Fistula.—An adult male patient had persistent small hemoptyses. Bronchoscopy showed tuberculous involvement of the right main bronchus with obstruction of the middle lobe. After five years, the hemoptyses became very severe and resection was done. Because of dense adhesions, a pneumonectomy was required. Examination of the specimen showed a fistula between the middle lobe bronchus and the corresponding branch of the pulmonary artery. Microscopic examination showed chronic inflammation probably originating in a lymph node.—*Pneumonectomy in a case of fistula between the middle lobe artery, F. Soave, Thorax, March, 1950, 5: 90.*—(*A. G. Cohen*)

Open Extrapleural Pneumonolysis.—In 4 cases, adhesions unsuitable for thoracoscopic division were freed by an extrapleural approach through the periosteum of the fourth rib posteriorly. The disc of parietal pleura over the adhesion was dropped into the pneumothorax cavity and in 2 of the cases the parietal pleural defect was sutured. Results were excellent in contrast to those in attempted maintenance of combined intra- and extrapneumothorax in which further adhesions usually form.—*Decollation of intrapleural adhesions by open extrapleural pneumonolysis, B. C. Thompson, J. Thoracic Surg., August, 1949, 18: 496.*—(*R. E. MacQuigg*)

Extrapleural Pneumonectomy and Pleurectomy.—The indications for resectional surgery in pulmonary tuberculosis are: (*1*) thoracoplasty failures; (*2*) thoracoplasty failure anticipated because of (a) predominantly pulmonary disease with a destroyed lung, a giant cavity, multiple cavities, or an inspissated cavity, (b) predominantly bronchial tension cavities and bronchial strictures, (c) predominantly pleural empyema, or (d) disease unfavorably located, with cavities in the paravertebral segment of the upper lobe, lingula of left upper lobe, middle lobe or lower lobes; and (3) emergency resection for uncontrollable hemorrhage or acute rupture of a cavity. Particular emphasis is placed upon extrapleural pleuropneumonectomy in the predominantly pleural group, *viz.*, cases with empyema. Previous methods of treatment by drainage and thoracoplasty or a Schede operation gave notoriously poor results. The author has demonstrated that the entire lung and involved pleura may be resected extrapleurally with safety and success. This has now been done for 18 cases with no mortality and minimal morbidity. The procedure is followed soon after by a thoracoplasty with infolding of mus-

cular flaps to help fill the dead space. The technique is described completely. It is advantageous to use a mediastinal approach in order to establish an extrapleural cleavage plane. In cases of early tuberculous empyema with localized cavitary tuberculosis, lobectomy or segmental resection combined with decortication is advocated if measures to re-expand the lung are not promptly successful. Contralateral disease, if quiescent or controlled by pneumothorax, is not a contraindication to resection. Neither is active involvement of the bronchus in the region where transection is to be done. Post-pneumonectomy empyema with a bronchopleural fistula may also be treated by pleurectomy. Streptomycin is given daily for one to three weeks before and three weeks after the operation.—*Extrapleural pneumonectomy and pleurectomy in pulmonary tuberculosis, I. A. Sarot, Thorax, December, 1949, 4: 173.* (*A. G. Cohen*)

Monaldi Drainage.—There were 100 tuberculous cavities in 90 patients accepted for treatment by intracavitary drainage between 1940 and 1947. Contraindications were history of profuse hemorrhage, free pleural space, a cavity too small to enter with trocar or too near the hilum, and multiple cavitation too extensive for relief even with successful drainage of one or 2 cavities. Usually the intercostal muscles were resected with a section of the first and sometimes of the second rib. Sulfanilamide crystals were sprinkled on the endothoracic fascia and the skin closed after packing with gauze. The pack was removed after 5 days. If thoracoplasty was to follow none or only a small piece of the second rib was removed, as the ultimate collapse might otherwise be retarded by regeneration of anterior segments which are better left for removal through a small separate anterior incision. Insertion of the catheter under fluoroscopic control was advised, two or three weeks after the packing, using the Kupka modification of the Monaldi trocar. The catheter was secured to the skin by a clove hitch of heavy silk fastened with adhesive, which held the catheter without compressing the lumen. Complications included bleeding (20 per cent, with one fatal case) and pneumothorax (8 per cent, with one fatal case). There was one air embolus with temporary hemiplegia. Two patients had 4 attempts at introduction of the trocar. Suction was not applied for 24 hours and thereafter suction equal to 20 or 30 cm. of water was maintained constantly. If there was frank bleeding, suction was discontinued for one or two days. Occasionally development of a chest wall abscess around a catheter was treated with incision and drainage. Catheters usually were replaced monthly. Forty (49 per cent) of the 82 cavities into which catheters were inserted finally closed; 33, within six months. As a rule there was almost immediate marked clinical improvement. In 11 cases the cavities reopened in three to four months. It is logical to perform thoracoplasty when possible rather than trust that the cavity will remain closed. Intracavitary drainage is useful both as a palliative and in preparing certain patients for collapse therapy.—*Review of seven years' experience with intracavitary (Monaldi) drainage of tuberculous cavities, W. Woodruff, W. O. Kelley, & A. Stranahan, J. Thoracic Surg., December, 1949, 19: 777.*—(*R. E. MacQuigg*)

Lactation after Thoracic Operations.—In 10 nonpuerperal women, lactation appeared after thoracic operations; in 9, following thoracoplasty; and in one, following pneumonectomy. Some lactogenic factor usually results from mechanical stimulation of the nerves of the breast by the act of suckling; in these women, the stimulation may have been supplied by the operation. It is possible that the lactogenic hormone may be present normally during the menstrual cycle and nonpuerperal lactation has been described frequently. In rarer cases it has followed stimulation of the breast in virgins and after a severe burn of the breast, after carcinoma of the pituitary gland, and at the time of menstruation. It has occurred even in men with disease of the genitals or following prolonged suckling of the breast. The literature contains no references to milk secretion following thoracic surgery.—*Lactation*

following thoracoplasty and pneumonectomy, D. Salkin & E. W. Davis, J. Thoracic Surg., August, 1949, 19: 580.—(R. E. MacQuigg)

CLINICAL STUDIES, NONTUBERCULOUS DISEASES

Constrictive Pericarditis.—To the 265 recorded operations for constrictive pericarditis, 9 cases are added with one death and marked improvement in the others. Adequate pericardiectomy must include liberation of all borders of the heart and both venae cavae. The pericardium lying between the heart and the diaphragm must be excised. In order to provide adequate exposure of the right cardiac border, which is the most important area and the most dangerous dissection, a median sternotomy with transverse division of the sternum in the second interspace is recommended. The sternum is reapproximated by several stainless steel sutures inserted through bone, not through avascular cartilage. The wound should be drained, preferably into the right pleural space from which the fluid can be removed either by aspiration or by intercostal drainage. Operation should not be deferred unduly if the symptoms of compression are incapacitating, unaffected by therapy, and progressive. Persistence of ascites following pericardiectomy is evidence of inadequate decortication and demands reoperation and removal of more scar rather than an omentopexy or Talma operation.—*The recognition and correction of constrictive pericarditis, E. Holman, J. Thoracic Surg., October, 1949, 19: 643.—(R. E. MacQuigg)*

Tussive Syncope.—A 42-year-old man experienced episodes of fainting following attacks of coughing. Performance of the Valsalva maneuver was followed by a grand mal convulsion. During cough the pressure in the right ventricle was found to be as high as 250 mm. of mercury; following the coughing spell it dropped to 50 mm. of mercury. The pressure in the right ventricle during coughing and during the Valsalva maneuver was lower following the intravenous administration of either tetraethylammonium chloride or aminophylline. Bronchoscopic intubation of the trachea failed to prevent the high pressures which occurred in the right ventricle with coughing. A 49-year-old man gave a similar history. Pressures up to 270 mm. of mercury were found in the right ventricle during coughing. In both patients, coughing and the Valsalva maneuver decreased ver ous return, pulmonary circulation, and car liac output. In addition, congestion of the cerebral veins and anoxemia occurred. The possibility of a reflex spasm of the pulmonary artery existed. "Tussive syncope" is a better term for this syndrome which was formerly called "Laryngeal epilepsy".—*Tussive syncope. Observations on the disease formerly called laryngeal epilepsy, with report of two cases, W. S. McCann, R. A. Bruce, F. W. Lovejoy, Jr., P. N. G. Yer, R. Pearson, E. B. Emerson, G. Engel, & J. J. Kelly, Arch. Int. Med., December, 1949, 84: 845.—(G. C. Leiner)*

Complications of Shock Therapy.—In 3 patients receiving insulin shock therapy pulmonary complications occurred; serial roentgenograms were taken. Two of these patients showed widely disseminated patches of infiltration and congestion consolidation of the right upper lung field. All 3 cases were characterized by rapid resolution of the pulmonary pathologic process. Clinical and experimental studies suggest that 3 major factors, alone or in combination, may cause such pulmonary complications. They are (*1*) aspiration of infectious material, (*2*) direct or indirect interference with cardiac function, and (*3*) interference with the function of the pulmonary and cardiac centers in the medulla.—*Pulmonary complications of insulin shock therapy, R. J. Gross & F. H. Schaefer, Am. J. Roentgenol., February, 1950, 63: 191.—(T. H. Noehren)*

Pathology of Pulmonary Beryllosis.—The problem of correlating the clinical signs and symptoms of chronic pulmonary beryllosis with the gross and histologic abnormality seems to be comparatively simple. The extent of pulmonary damage involving alveoli, atria,

alveolar ducts, bronchioles, blood vessels, and lymphatic channels appears to be quite adequate to explain the complete clinical syndrome. Grossly the lungs appear to be involved in a long-standing, bilateral, granulomatous, inflammatory reaction which is most marked in the lower lobes. Great destruction of lung parenchyma, severe emphysema, and irreparable loss of much of the capillary bed are found. Microscopically, 5 distinct lesions usually can be demonstrated, namely: (*1*) a focal granulomatous reaction composed largely of epithelioid cells with occasional multinucleated giant cells, which is the most characteristic, striking, and destructive of the 5 lesions and is responsible for the name "focal granulomatous pneumonitis"; (*2*) a nonspecific, chronic, interstitial, inflammatory reaction dominated by a proliferation of granulation tissue rich in lymph follicles, lymphocytes, and plasma cells; (*3*) a serous reaction of the interstitial tissue; (*4*) a catarrhal or desquamative reaction in the alveolar spaces, and (*5*) an unusual proliferative reaction over the surface of the visceral pleura. None of these alone is specific.—*Chronic pulmonary beryllosis in workers using fluorescent powders containing beryllium, H. E. MacMahon & H. G. Olken, Arch. Indust. Hyg. & Occup. Med., February, 1950, 1: 195.*—(*T. H. Noehren*)

Respiratory Disease in Cement Workers.—Physical and roentgenological examinations were carried out on 2,837 of 3,393 workers in 10 cement factories in Argentina. In these factories there was an average of 5,578,820 dust particles per cubic foot, as compared to 26 million per cubic foot found by the Public Health Service in factories in the United States. Sanitary conditions did not correlate with the amount of respiratory disease present. The factory with the smallest amount of dust showed the highest rates of both catarrhal bronchitis and of chronic bronchitis with emphysema (13.3 per cent each). One of the lowest incidences of chronic bronchitis with emphysema (3.2 per cent) was found in the factory with the highest dust count. This supports the view that other factors, especially the length of exposure, influence the results. Disseminated pulmonary sclerosis (peribronchovascular fibrosis of the lung) which may be related to the inhalation of irritating or poisonous dusts was found in only 3.59 per cent of the group examined. This is lower than among the general population, and is especially remarkable since more than 20 per cent of these men have worked in the industry more than eleven years. A significant correlation was found between the number of dust particles in the factory air and the incidence of chronic rhinitis among the personnel. The absence of silicotic pulmonary fibrosis among cement workers was confirmed. A possible explanation is that dust particles impinge upon the nasal mucous membrane, and fail to reach the lung alveoli in an active state.—*Higiene y salubridad en la industria del cemento porland, R. A. Vaccarezza, Rev. argent. de tuberc., 1949, 13: 9.*—(*A. A. Moll*)

Pulmonary Function in Silicosis.—The degree of emphysema as measured by expressing residual air as percentage of total lung volume is a very significant measurement in the evaluation of disability and, if the residual air is markedly increased, this factor alone may be adequate to produce complete disability for work requiring increased consumption of oxygen. In general, as the residual air and the emphysema increase, the maximal breathing capacity and the vital capacity decrease. As single measurements, maximal breathing capacity and vital capacity are of limited use in the evaluation of pulmonary function. Maximal breathing capacity may be used in screening tests for detecting early evidence of fibrosis with loss of lung elasticity. A sharp decrease in the oxygen saturation of arterial blood with mild exercise is a second very significant measurement in the evaluation of disability, for it indicates a greater disproportion between the ventilation and perfusion ratios when the consumption of oxygen is increased by work. The respiratory gas exchange measurements may be essentially normal at rest and yet show gross abnormalities during exercise

In approximately 30 per cent of the cases of anthracosilicosis the residual air percentage of total lung volume was within the normal range. The disability present in these cases resulted from the fibrosis and the accompanying inequality of alveolar aeration and perfusion which decreases the amount of oxygen reaching the arterial blood (the distribution factor). The distribution factor was present in most cases of anthracosilicosis, regardless of the degree of emphysema. The present studies indicate that for the most part the difficulty of the transfer of gases between the alveoli and the blood results from poor distribution, rather than from a true difficulty of diffusion with increased resistance of the pulmonary membrane. The percentage of oxygen taken from, and the percentage of carbon dioxide added to, the air breathed are helpful in the over-all evaluation of the impairment present, but have slight value as single measurements. Strain on the right side of the heart as indicated by electrocardiographic changes is found only in cases with a significant degree of emphysema and, as the degree of emphysema increases, a greater incidence of the strain is noted. There is no apparent correlation between the roentgenographic stage of silicosis and the degree of impairment of pulmonary function in many cases. In some cases extensive effects of anthracosilicosis were visualized on the roentgenogram when pulmonary function was only slightly involved, while in other cases with minimal roentgenologic changes the pulmonary function was greatly altered. An accurate evaluation of the degree of impairment of pulmonary function requires measurements of ventilation, residual air, oxygen uptake from the air breathed, oxygen saturation of arterial blood and pulmonary circulation. The wide individual variations encountered in these determinations preclude the using of any one single measurement as satisfactory for the appraisal of disability in all types of cases (Authors' summary).—*Impairment of pulmonary function in anthracosilicosis, H. L. Motley, B. Gordon, L. P. Lang, & P. A. Theodos, Arch. Indust. Hyg. & Occup. Med., February, 1950, 1: 133.*—(*T. H. Noehren*)

Occupational Lipid Pneumonia.—Seventeen years of exposure to grade 10 liquid petrolatum ("mineral oil") in spraying cash registers produced what is thought to be the first reported case of occupational lipid pneumonia. The chief complaints were cough, shortness of breath, and a sense of fatigue associated with gradual weight loss. The cough produced one to two tablespoons per day of thick mucoid sputum. The posterior-anterior roentgenograms of the chest showed soft shadows radiating from the hilus into both right and left mid-lung fields. These shadows were evenly distributed following the anatomic distribution of the bronchi for the most part. They were similar to those produced by lipiodal several days after the oil had been introduced. The upper lung fields were relatively free from any unusual markings. The sputum contained large numbers of oily or fatty globules which were mostly extracellular; a few were within macrophages. The very slight change in the roentgenogram taken four years later was thought to support the diagnosis of chronic lipid pneumonia.—*Chronic lipid pneumonia following occupational exposure, J. P. Proudfit, H. S. Van Ordstrand, & C. W. Miller, Arch. Indust. Hyg. & Occup. Med., January, 1950, 1: 105.*—(*T. H. Noehren*)

Cholesterol in Interstitial Pneumonitis.—Ten cases of chronic nonsuppurative interstitial pneumonitis treated by resection were characterized by high parenchymal concentrations of cholesterol and by cholesterol esters in the mononuclear cells of the exudate. Cholesterol pneumonia is found not uncommonly in the presence of stenosis of the major bronchus. Biopsy and frozen sections at the time of opertion are of uncertain value since the microscopic changes may be the result of bronchial stenosis from tumor. In the 10 cases, bronchial stenosis could not be demonstrated before operation, at operation, or in the resected lobe. It is possible that during the initial pneumonia a viscid exudate resulted in prolonged obstruction of the bronchioles with partial destruction and ectasia, chronic pneumonitis, and parenchymal fibrosis of the sec-

ondary lobules beyond the obstruction. It is presumed that successive waves of secondary infection continually irritated the diseased parenchyma. Widespread necrosis of tissue or continued exudation of plasma into the alveoli are possible sources of the cholesterol but tissue necrosis was not apparent in the diseased parenchyma nor are similar changes found in chronic pulmonary edema. For the moment, the origin of the cholesterol remains an intriguing mystery.—*Chronic pneumonitis: its clinical and pathologic importance. Report of ten cases showing interstitial pneumonitis and unusual cholesterol deposits, W. R. Waddell, R. C. Sniffen, & R. H. Sweet, J. Thoracic Surg., October, 1949, 18: 707.*—(*R. E. MacQuigg*)

Chronic Pneumonitis of Middle Lobe.—In the past three years 32 patients with chronic atelectasis and pneumonitis of the right middle lobe have been seen. Right middle lobectomy was performed in 29. Review of the cases revealed a characteristic diagnostic pattern which permitted accurate preoperative diagnosis. The essential pathology was bronchial obstruction. Enlarged and inflamed peribronchial lymph nodes have been found in 15 patients; in another 8, large calcified nodes were encountered. In 6 patients the obstruction was apparently produced by inflammation of the bronchial wall only. At operation complete atelectasis was found in 14 patients and partial atelectasis in 12. The results of operation were satisfactory on the whole. A right lateral roentgenogram was necessary to identify these cases properly. Any patient with chronic cough accompanied by right anterior chest pain, hemoptysis, a history of recurrent pneumonias, low-grade fever, and easy fatigability should be considered as possibly having this disease. A complete bronchogram should be made in all cases, so that the remainder of the bronchial tree may be studied as well as that of the middle lobe. The syndrome is presented as a newly recognized clinical entity which cannot be classified as bronchiectasis or as a lung abscess. Mechanical factors tend to favor bronchial obstruction of the right middle lobe. Graham, Burford, and Mayer in 1947 believed "the middle lobe syndrome" to be a clinical entity. The most important condition in the differential diagnosis is bronchiogenic carcinoma. The treatment is surgical. Pulmonary emphysema probably will develop if the localized pneumonitis is allowed to persist.—*Chronic atelectasis and pneumonitis of the middle lobe, D. L. Paulson & R. R. Shaw, J. Thoracic Surg., December, 1949, 18: 747.*—(*R. E. MacQuigg*)

Pulmonary Changes in Scleroderma.—It now is realized that scleroderma is not a local skin disease but is a systemic disorder with involvement of many organs, among them the lungs. In previously reported cases with pulmonary involvement, the chief clinical features are dyspnea and unusual susceptibility to respiratory infections. The roentgenographic features have been described as extensive fibrosis, especially of the lower lobes. The histologic changes are basically vascular with endarteritis and fibrinoid necrosis of vessel walls and surrounding collagen tissue; the fibrosis is secondary. In 2 additional cases cystic changes as well as fibrosis were seen in the roentgenograms.—*Cystic pulmonary fibrosis in generalized scleroderma, R. E. Church & A. R. P. Ellis, Lancet, March 4, 1950, 1: 392.*—(*A. G. Cohen*)

Arteriovenous Aneurysm.—Two cases of pulmonary arteriovenous aneurysms in association with familial hemorrhagic telangiectases are reported. In the first case, in addition to superficial telangiectasis of the skin, tongue, and mucous membranes of the mouth, there were demonstrated by gastroscopy numerous telangiectatic lesions of the stomach which were thought to be the source of repeated gastric hemorrhages. Chronic anemia was a prominent finding and was attributed to chronic blood loss from repeated epistaxis and hematemesis. The pulmonary arteriovenous aneurysm was demonstrated by the method of angiocardiography to be located in the left lower lobe adjacent to and partially overlying the cardiac apex. Confusing auscultatory find-

ings were present and were difficult clinically to distinguish from those of intrinsic cardiac valvular disease. Spleen and liver were palpable. Cyanosis and polycythemia were apparently obscured by blood loss anemia but both appeared after a hemorrhage-free period. Arterial blood oxygen saturation was reduced. In the second case there were telangiectases present on the skin of the hands, face, and feet as well as on the buccal and nasal mucous membranes. The arteriovenous aneurysm was demonstrated by angiocardiography to lie in the posterior portion of the apex of the right lower lobe. The patient was cyanotic with early clubbing of the fingers, although definite polycythemia with increased blood volume was not substantiated by laboratory studies. Arterial blood oxygen saturation was, however, reduced (Authors' summary).—*Familial hemorrhagic telangiectasia with associated pulmonary arteriovenous aneurysm, H. L. Armentrout & F. J. Underwood, Am. J. Med., February, 1950, 8: 246.*—(*T. H. Noehren*)

Pulmonary Embolism from Saphenous Vein.—Venous thrombosis of the lower extremities has been divided into 2 types: (*1*) Phlebothrombosis usually occurs in the deep veins. The intravascular clot is associated with minimal intimal inflammation so that the clot is not adherent and embolism is common. (*2*) Thrombophlebitis more commonly occurs in the superficial veins. The inflammation of the intima is severe so that the clot is adherent and embolism is less common. It is probable that these types are but 2 stages of the same disorder. It is usually held that when embolism occurs in the presence of a superficial thrombophlebitis, the embolus arises from phlebothrombosis in the deep venous system because of the immobilization of the limb during treatment of the superficial venous disorder. In the case reported, pulmonary embolism arose from an area of phlebothrombosis in the great saphenous vein. The phlebothrombosis developed in a normal segment of vein proximal to an area of pre-existent thrombophlebitis but clots were not in continuity. The diagnosis was established by operation and the patency of the deep system was confirmed by venography. It is suggested that early ligation and division of the superficial saphenous vein at the groin should be the treatment of saphenous thrombophlebitis.—*Pulmonary embolism arising from the great saphenous vein, E. T. McCartney & A. S. Lewis, Brit. J. Surg., July, 1949, 37: 45.*—(*M. G. Carter*)

Bronchoscopy for Allergic Asthma.—A total of 112 asthmatic patients have had therapeutic bronchoscopies. The bronchial obstruction in asthma is caused by mucus as well as spasm, and as the mucus becomes dry and thick the condition becomes more severe and protracted. Bronchoscopy should be employed: (*1*) to prevent a moribund patient from becoming asphyxiated by mucus; (*2*) to break up a status asthmaticus, regardless of its severity; (*3*) to remove a plug causing atelectasis; (*4*) to dilate strictures; and (*5*) to remove secretion from bronchiectatic areas. Eight of the patients in this series were moribund when treated. In all but one the main bronchi were partially obstructed by mucus plugs and the asthma subsided after removal of 30 to 60 cc. of this material through aspiration and lavage with saline solution. Bronchography is dangerous; bronchoscopy should not be employed when there is minimal or thin secretion. Hazards lie in systemic or local intolerance to anesthetics. Opiates, including Demerol, aggravate the condition. Little or no anesthesia should be employed. One-half of a 0.24 gm. ampule of aminophyllin and 0.05 cc. of 1:1,000 epinephrine are given intravenously before bronchoscopy with another half-ampule of aminophyllin held in reserve. Both history and interdermal skin tests are checked for sensitivity to penicillin before bronchoscopy, as penicillin in saline may be warranted by marked inflammation of the bronchial mucosa.—*Use and abuse of bronchoscopy in allergic asthma, G. I. Waldbott, J. Thoracic Surg., August, 1949, 18: 526.*—(*R. E. MacQuigg*)

Tube for Tracheal Aspiration.—Comatose or semi-comatose patients and some postoperative patients accumulate tracheobronchial

secretions which result in atelectasis and fatal pneumonia if not removed. A double lumen catheter has been devised for the continuous administration of oxygen and simultaneous suction endotracheally. The tube may be passed blindly while the patient is in bed on the ward and may be used either intermittently or as an inlying endotracheal tube. The double lumen tube has been used with 60 patients and no complications attributable to its use have been noted.—*A double lumen intratracheal tube for simultaneous ozygen administration and tracheobronchial aspiration, R. A. Buyers, Surgery, January, 1950, 27: 74.*—(*M. G. Carter*)

Scale for Measuring Blood Loss.—If too much blood is infused during an operation the heart may fail; if too little is given the patient may develop serious shock. It is desirable to have a rough method for immediate guidance and for this, weighing of used sponges may be employed. Dry sponges of a standard variety uniformly weigh 8 gm.; dry pads, 40 gm. It is, therefore, unnecessary to weigh the particular sponges before use. An ordinary dietetic scale is remodeled with the face so calibrated that it may be rotated to the number of sponges being weighed and the volume of blood in the used sponges may then be read against the scale pointer. The circulating nurse keeps a rough balance sheet so the surgeon may be told instantly how much blood has been lost and how much infused. The scale is obviously useful in any field where blood loss is apt to be high.—*A scale for rapid measurement of blood which is lost in surgical sponges, R. E. Gross, J. Thoracic Surg., August, 1949, 18: 543.*—(*R. E. MacQuigg*)

Tracheal Carcinoma.—Primary carcinoma of the trachea is relatively rare. The recorded cases indicate an even distribution between the ages of 30 and 70 years; over 60 per cent occur in males. The tumors most commonly arise in the lower one-third of the trachea, at or near the bifurcation. Squamous cell carcinoma is the most common cell type, occurring in 35 per cent of the reported cases classified histologically, but adenocarcinoma and undifferentiated carcinoma also occur. These cell types are similar to those of primary bronchogenic carcinoma. Two cases of primary tracheal carcinoma occurring in elderly males are reported. In each, the lesions occurred in the upper one-third of the trachea and death was due to partial respiratory obstruction and diffuse bronchopneumonia. Autopsy revealed "oat-cell" carcinoma with widespread metastases in one case and squamous cell carcinoma with local lymphatic spread in the other.—*Primary carcinoma of the trachea, J. F. Pantridge, Brit. J. Surg., July, 1949, 37: 48.*—(*M. G. Carter*)

Pneumonectomy for Carcinoma.—Routine skeletal survey for metastasis has been eliminated, as skeletal metastasis from pulmonary carcinoma almost invariably makes its presence suspected by pain. Cardiac survey, including electrocardiogram, is essential. Recently circulation time and an overload test have been included. The overload test is done by introducing 10 cc. of saline per pound of body weight into the venous circulation in 30 minutes. Venous pressures and circulation time are taken before and after introduction of the fluid. If the patient develops any untoward symptoms, fluid is stopped immediately. Thoracoplasty has been done at a later period only on patients developing empyema. The authors' present operative mortality is approximately 20 per cent and is largely from cardiac failure. Since hilar lymph nodes were involved in only 18 of the 67 patients undergoing pneumonectomy, lobectomy should be strongly considered in certain peripheral lesions, unless the mortality of pneumonectomy can be lowered. In the cases followed from six to ninety-nine months, the salvage was 32.9 per cent, which compares favorably with the treatment of carcinoma of the stomach.—*Carcinoma of the lung: a follow-up on sixty-seven patients subjected to pneumonectomy, W. E. Burnett, G. P. Rosmond, & J. H. Hall, J. Thoracic Surg., October, 1949, 18: 679.*—(*R. E. MacQuigg*)

Lobectomy for Coccidioidomycosis.—Two cases are discussed in which cavitation finally occurred following primary asymptomatic coccidioidomycosis. Only 2 cases of lobectomy for this disease have been reported previously. Lobectomy in one of the present cases rendered the sputum negative. In the other case cough and fatigue developed a year later and a cavity was found in the remaining lower lobe. This was treated by thoracoplasty and cavernostomy. Tubercle bacilli and coccidioidal spherules were found in this cavity. Lobectomy should prevent spread of the disease to other parts of the body and also eliminate the danger of hemorrhage. Dissemination is usually fatal and hemoptysis may be. However, in some reported instances of cavitation, patients have continued to work and the cavities have closed without any treatment.—*Lobectomy in coccidioidomycosis, J. A. Moore, J. D. Murphy, & D. E. Ward, Jr., J. Thoracic Surg., August, 1949, 18: 484.—(R. E. MacQuigg)*

Surgery for Focalized Coccidioidomycosis.—Of 13 patients with focalized coccidioidomycosis, 9 had lobectomy for persistent cavitation and 4 had wedge resections of rounded granulomas. The patients with cavitation noted cough and weakness; 5 had hemoptysis and 3 had chronic low fever and weight loss. The patients with granulomas were asymptomatic. The mycelial form of the organism was found in 6 of the cavities. The reason commonly proposed for lack of human transmission has been that the spherule form of the organism which is usually seen in the sputum, exudates, and diseased tissue has a low infectivity. Cavities may, therefore, permit infection of others. In 4 cases previously presented, rupture of the lesion has caused bronchopleural fistula, coccidioidal empyema, and nonexpansile lung. Despite these considerations it is suggested that resection be reserved for patients with definite symptoms over a long period. Results have been good in all but 2 of the 13 cases. One patient developed tuberculosis in the remaining lower lobe three months after resection of the upper lobe. Another case was asymptomatic for two years after resection, when suddenly the symptoms returned and a 3 cm. cavity appeared in the remaining lower lobe. It may be that longer hospitalization, both before and after surgery, would be beneficial.—*The surgical management of pulmonary coccidioidomycosis in localized lesions, S. J. Greer, J. H. Forsee, & H. W. Mahon, J. Thoracic Surg., October, 1949, 18: 591.—(R. E. MacQuigg)*

Pulmonary Resection for Lung Abscess.—The classification of lung abscesses into simple and complicated, rather than acute and chronic, is recommended. The simple abscess is a single cavity without extensive pneumonitis, fibrosis, or bronchiectasis. While adequate drainage of simple lung abscesses may result in cure, draining the major focus of a complicated abscess leaves significant pulmonary disease present. Adequate localization of the cavity with lateral and oblique as well as the usual anterior-posterior roentgenograms is important. Bronchoscopy must be done promptly and bronchography is important in identifying obstruction beyond the endoscopically visible areas and in indicating bronchiectasis. Of 38 patients operated upon at Fitzsimons General Hospital between September 1942 and September 1947, 36 had complicated abscesses. Since bronchoscopic examination of the upper lobe bronchi is decidedly limited and, since the various studies have shown from 12 to 48 per cent of pulmonary carcinoma with cavitation, lung abscesses occurring in upper lobes should be treated by resection, particularly in the older age groups. The mortality rate in the 38 cases was less than 8 per cent.—*Pulmonary resection for lung abscess, A. J. Neerken & J. B. Grow, J. Thoracic Surg., October, 1949, 18: 738.—(R. E. MacQuigg)*

Pulmonary Function after Pneumonectomy.—Respiratory function was compared before and after pneumonectomy in 24 patients. There was little or no change in the over-all resting tidal volume, minute volume, and oxygen consumption. The maximum breathing capacity and the breathing reserve usually

were diminished by reduction in the depth of respiration during maximum respiratory effort. The lack of change in the over-all resting pulmonary function was due to compensatory adjustments of the remaining lung, namely, an increase in tidal volume, an increase in minute volume, and in oxygen uptake. What increase occurred in the maximum breathing capacity of the remaining lung was due to an increase in the rate of respiration.—*The effect of pneumonectomy on pulmonary function, W. E. Burnett, J. H. Long, C. Norris, G. P. Rosemond, & M. R. Wester, J. Thoracic Surg., August, 1949, 18: 569.*—(*R. E. MacQuigg*)

Thoracic Waist.—In the majority of adults a circumscript retraction of the lateral rib segments can be found at the level of the sixth to eighth ribs. The impression or furrow produced thereby is termed the thoracic waist. The deformity starts to develop first at the end of adolescence, and both its frequency and depth increase with age. Unilateral development of the thoracic waist occurs frequently. It must be strictly differentiated from localized pathologic retractions of the chest wall.—*The "thoracic waist," F. Polgar, Am. J. Roentgenol., March, 1950, 63: 345.*—(*T. H. Noehren*)

Bronchopulmonary Segments.—Recent advances and refinements of surgical techniques in segmental pneumonectomy have emphasized the need for the roentgenologist to be thoroughly familiar with pulmonary segmental anatomy. Frequent variations in the segmentation of the bronchial tree and variations in the individual segments require careful roentgenologic studies and close cooperation between bronchoscopist and roentgenologist. The lack of a uniform nomenclature acceptable to roentgenologist, surgeon, internist, bronchoscopist, and anatomist has resulted in a certain amount of confusion. The terminology suggested by Jackson and Huber is best suited to meet the practical needs of the roentgenologist. The anatomy of the bronchial tree and bronchopulmonary segments can be correlated with the roentgenographic features of pulmonary segmental lesions (Authors' summary).—*The bronchopulmonary segments, H. L. Temple & J. A. Evans, Am. J. Roentgenol., January, 1950, 63: 26.*—(*T. H. Noehren*)

Accessory Lobe.—In the lungs of approximately 10 per cent of normal individuals the lower lobe is divided medially to form an accessory lobe which may be either unilateral or bilateral. On "normal" chest roentgenograms, recognition of this lobe is dependent on the visualization of its interlobar pleura. This appears as a fine linear density extending from the medial portion of the diaphragm obliquely upward and medially toward the hilum of the lung. At the origin of the pleura from the diaphragm there is frequently a small "diaphragmatic tent" which may be mistaken for an adhesion. In one case densities due to congestion and edema of the inferior lobe and to localized pleuritis with effusion were associated with an acute nephritis. Thus, another lesion must be considered in the differential diagnosis of densities in the cardiophrenic angle.—*Pathological condition in an inferior accessory lobe and its pleura, J. W. Grossman & C. F. Fishback, Am. J. Roentgenol., January, 1950, 63: 47.*—(*T. H. Noehren*)

Angiocardiography.—Successful angiocardiography requires two conditions: (*1*) sufficient dye must be moved rapidly into the zone to be visualized by very rapid intravenous injection of 40 to 50 cc. of 70 per cent Diodrast or 75 per cent Neoiopax in adults. The needle should be only slightly smaller than the vein used. (*2*) The equipment must be capable of a rapid sequence of radiographic exposures. The rapidograph, a modification of the aerial camera of the Fairchild Camera and Instrument Company, is now used to make exposures every half second. Retrograde arterial technique is valuable in cases of lesions of the aorta or its immediate branches. One common carotid, usually the left, is surgically exposed and a large cannula introduced toward the heart between ties, under a third tie to prevent leakage. After releasing the proximal tie the dye is introduced. The proximal ligature is again tied and the needle removed. Two deaths occurred

in 86 visualizations. In 23 of those which were by the retrograde method, there have been no complications attributable to the sacrifice of the carotid artery. It is stressed that angiocardiography is not to be recommended in every case of congenital cardiovascular heart disease since it is not a method without hazard. The diagnosis can be made confidently in most instances by simple examination and fluoroscopy.—*Angiocardiography and aortography in the diagnosis of congenital cardiovascular lesions, T. H. Burford, M. J. Carson, & W. G. Scott, J. Thoracic Surg., December, 1949, 18: 860.*—(*R. E. MacQuigg*)

Angiocardiography and Venography.—Mediastinal or paramediastinal masses were studied in 36 cases by means of angiocardiography, venography, or both. Angiocardiography is necessary for all lesions of the middle mediastinum and of almost equal importance for lesions of the superior mediastinum, especially those located in the right paramediastinal area. It is essential that careful fluoroscopy and multiple roentgenographic studies be carried out before determining the particular positions and combinations of angiocardiographic methods to be utilized in each case. Angiocardiography can be of specific value as an aid in the study of bronchiogenic carcinoma, especially in the upper lobes. Postmortem studies show a specific distortion of the vascular pattern in advanced pulmonary emphysema of the type known as "vanishing lung disease" but there are apparent inherent dangers of angiocardiography for this type of patient.—*The role of angiocardiography and venography in mediastinal and paramediastinal lesions, O. A. Abbott, W. A. Hopkins, & T. F. Leigh, J. Thoracic Surg., December, 1949, 18: 869.*—(*R. E. MacQuigg*)

ECG in Acute Cor Pulmonale.—The electrocardiographic diagnosis of acute cor pulmonale was made in 8 and favored in a ninth patient studied with standard and unipolar limb and chest leads and subsequently examined post mortem. In 7 of these the diagnosis was confirmed pathologically. In this group the diagnosis could often be made on the basis of changes in the standard leads. The precordial leads frequently gave corroborative and occasionally decisive evidence for the diagnosis, the evidence consisting of inversion of T waves in one or more precordial leads, shift of the transitional zone to the left, and corroborative evidence of incomplete right bundle branch block. Unipolar limb leads were not apt to be so helpful. In 2 patients an abnormal Q wave was present in the unipolar left leg lead (aV_F). In these patients acute pulmonary embolism and not posterior myocardial infarction was found at autopsy. In the eighth patient the diagnosis of acute cor pulmonale was favored over posterior myocardial infarction because of an inconspicuous Q wave in aV_F, but autopsy showed an acute posterior myocardial infarct and no pulmonary embolism. One instance of acute cor pulmonale was associated not with pulmonary embolism but with massive pulmonary atelectasis. The electrocardiogram may give the first clue to the diagnosis of acute cor pulmonale. This electrocardiographic diagnosis can be made with a high degree of accuracy (Authors' summary).—*A critical evaluation of extremity and precordial electrocardiography in acute cor pulmonale, E. Phillips & H. D. Levine, Am. Heart J., February, 1950, 39: 205.*—(*G. C. Leiner*)

ANTIMICROBIAL THERAPY

Treatment of Tuberculous Meningitis.—A total of 43 patients with tuberculous meningitis was treated. Almost all were under seven years of age. Bacteriologic proof was obtained in 40 cases; this was accomplished by smear in 47 per cent, culture in 63 per cent and guinea pig innoculation in 88 per cent. Streptomycin was given only intramuscularly in 6 cases, all of whom succumbed. Combined intramuscular and intrathecal therapy was used in 37 cases, of whom 14 survive, including 8 with full recovery. The initial response to treatment depends upon several factors besides streptomycin such as age, virulence of organisms, and mechanical obstruction to the flow of cerebrospinal fluid. The proportion of full recoveries in any series depends more on the

number of cases with good initial response than on the particular rhythm of treatment. The best rhythm is a three-month course of combined intramuscular and intrathecal (not less than 50) treatments, followed by intramuscular administration alone until the cerebrospinal fluid has been normal on 2 occasions over a period of three months. Another rhythm used with success is to give much shorter courses of intramuscular and intrathecal therapy separated by rest periods during which intramuscular treatment is continued. Intrathecal therapy is resumed whenever the cerebrospinal fluid findings indicate a threatened recrudescence. With this rhythm, a high proportion of survivors and full recoveries can be obtained, but the treatment requires over a year and therefore is not favored.—*Tuberculous meningitis in children, D. MacCarthy & T. P. Mann, Lancet, February 25, 1950, 1: 340.*—(*A. G. Cohen*)

Streptomycin for Primary Tuberculosis.—In 22 cases of childhood tuberculosis the primary complex was visible roentgenographically. All the patients had positive tuberculin tests and positive gastric cultures for tubercle bacilli or had coexistent miliary or meningeal tuberculosis. Streptomycin was given for at least three months and observations were made for six additional months. It was concluded that the drug did not exert any beneficial effect as far as clearing of the lesion was concerned.—*Streptomycin and the primary lung lesion in tuberculosis in children, J. Lorber, Lancet, March 4, 1950, 1: 389.*—(*A. G. Cohen*)

Streptomycin Locally for Sinuses.—In 25 cases of bone and joint tuberculosis with discharging sinuses local instillations of streptomycin, 0.25 to 1.0 gm., were employed daily. In a few, sequestrectomy was done, but no other surgical treatment was given. After several months of treatment, the results were very good and were considered better than those achieved by intramuscular administration of the drug.—*Tuberculous sinuses treated by streptomycin locally, R. T. Ahern, Lancet, March 11, 1950, 1: 443.*—(*A. G. Cohen*)

Streptomycin Following Hemoptysis.—Seven patients with progressive tuberculosis as the result of recent posthemoptoic spreads were chosen for streptomycin therapy. Each by chance was given a different amount of streptomycin. As a result of this therapy 4 patients showed dramatic improvement, one moderate improvement, and the treatment in 2 failed completely. On the basis of the various dosage schedules used, a 42-day period of treatment with a daily dose of 1 gm. in a single injection is suggested as bacterial resistance generally does not develop during this period. In case of relapse, re-treatment is more likely to be effective.—*Streptomycin in pulmonary tuberculosis, N. C. Furtos, U. S. Armed Forces M. J., February, 1950, 1: 137.*—(*T. H. Noehren*)

Antituberculous Activity of Subtilin.—The degree of inhibition of tubercle bacilli by subtilin *in vitro* paralleled the degree of growth dispersion of the organisms. In a medium in which growth was clumped, whether because of omission of Tween or of antagonism of Tween by serum, no significant inhibition of growth by subtilin was demonstrated; high activity was found in media permitting diffuse growth. Sera from rabbits injected with subtilin inhibited growth of *Streptococci* and *Staphylococci* but not of tubercle bacilli unless sufficient Tween was present to permit diffuse growth of these bacilli. This phenomenon offers an explanation for the high inhibitory activity of subtilin on tubercle bacilli *in vitro* and the failure to protect experimentally infected animals.—*Relationship of type of growth of M. tuberculosis to antituberculous activity of subtilin, V. Knight & R. Tompsett, Proc. Soc. Exper. Biol. & Med., January, 1950, 73: 55.*—(*F. B. Seibert*)

Methods of Penicillin Administration.—The relative effectiveness of various methods of administering penicillin was determined in 4 patients with bronchiectasis or lung abscess. None of the patients showed detectable penicillin in the sputum after intramuscular injection of 100,000 units of penicillin. Inhala-

tion and intratracheal administration were more successful. A disadvantage inherent in the aerosol method is wastage, only 35 per cent of the penicillin being actually absorbed. The only force which carries the minute particles of aerosol into the lung is respiratory motion which is lost in deep suppurative foci. As it is not known how deeply aerosolized penicillin actually penetrates purulent cavities, endotracheal administration may be advantageous and the addition of wetting agents may increase the depth of penetration. It appears possible that a thick-walled hollow cavity could only be reached by a gravitational flow of penicillin, such as that which follows direct injection of fluid. Intratracheal therapy is recommended where intubation is necessary for other reasons such as at the time of bronchoscopy or bronchography, in thoracic surgery during routine postoperative tracheal aspirations to prevent atelectasis, and where rapid improvement and reduction of symptoms are necessary as before resection. In all other instances aerosolization appears to be the ideal method for the medical treatment of such purulent disorders of the lung.—*Relative effectiveness of parenteral, intratracheal, and aerosol penicillin in chronic suppurative disease of the lung, E. A. Gaensler, J. F. Beakey, & M. S. Segal, J. Thoracic Surg., August, 1949, 18: 546.*—(*R. E. MacQuigg*)

Penicillin for Lung Abscess.—A patient with a chronic lung abscess completely recovered with penicillin inhalation therapy. A total of 6,000,000 units of penicillin given intramuscularly, combined with several courses of sulfadiazine therapy, had failed to affect the course of the disease. The abscess cavity appeared to increase on this management. He was then given penicillin aerosol inhalations, 100,000 units five times daily. After ten days the patient became afebrile and expectoration diminished to less than 15 cc. per day. The inhalation therapy was continued for forty-two days with complete resolution of the pulmonary process. It is felt that this may constitute an important addition to the medical management of lung abscess.—*Aerosol penicillin in the treatment of chronic lung abscess, H. A. Bickerman, J. Stone, & A. J. Schilaro, Am. J. Med., February, 1950, 8: 263.*—(*T. H. Noehren*)

Aureomycin for Pneumococcic Pneumonia.—Aureomycin was administered to 20 male and 13 female patients with pneumococcic pneumonia. Their age ranged from 13 to 75 years. Various complicating conditions were present in 18 patients. Pneumococci were found in blood cultures from one-third of the patients. Most patients were moderately or severely ill; in 7 the illness was mild; one was almost moribund. The first dose of aureomycin was given in most instances on or before the fifth day of illness. It was administered by mouth in dosages from 1.0 gm. every four or six hours to 0.5 gm. every four, six, or eight hours. The total dose of 5.5 to 46.5 gm. was given over a period of two to fifteen days. Aureomycin was given parenterally to 6 patients, of whom 2 died within eighteen hours after the treatment was started. In all 31 patients who recovered there was a marked drop of temperature during the first two days after the administration of aureomycin was started, and there was usually an improvement in the acute symptoms. Marked improvement of pulmonary lesions was usually seen within six days after the initiation of treatment. Complete resolution was demonstrated in roentgenograms taken on or before the end of the second week of treatment. The results of treatment by the intravenous route, which was used in 4 patients, were similar to those observed in the patients who were given larger and more frequent doses by mouth. Toxic effects of aureomycin were: nausea and vomiting in 3, large and bulky stools in 7. The results are comparable to those in similar patients treated with penicillin.—*Aureomycin treatment of pneumococcic pneumonia, T. M. Gocke, H. S. Collins, & M. Finland, Arch. Int. Med., December, 1949, 84: 857.*—(*G. C. Leiner*)

Aureomycin for Pulmonary Infections.—Aureomycin alone was highly effective in the treatment of a group of 13 cases of acute bac-

terial, nonpneumococcic pneumonias. Most of these cases probably occurred as complications of influenza viral infections. The effects of aureomycin therapy in 20 cases of nontuberculous bacterial bronchopulmonary infection were variable. The best effects were observed in cases in which aureomycin-susceptible organisms were primarily concerned. The beneficial effects were limited, however, because of the replacement of some of these susceptible organisms by relatively resistant ones. In almost all of these cases the aureomycin was started after other antibacterial agents had been given without effect or with only limited benefit. Subsequent use of similar antibacterial agents in most of these cases, including chloramphenicol in 4, failed to produce any further appreciable beneficial effects (Authors' summary).—*Aureomycin therapy of nonpneumococcic and nontuberculous bacterial pulmonary infections, H. S. Collins, T. M. Gocke, & M. Finland, Arch. Int. Med., December, 1949, 84: 875.—(G. C. Leiner)*

Antimicrobial Action of Terramycin.—Terramycin has a strong antimicrobial activity *in vitro* against a wide variety of aerobic and anaerobic gram-positive and gram-negative bacteria and against certain of the rickettsiae. There appears also to be some tuberculostatic effect *in vitro* and a chemotherapeutic action against experimental mouse infections due to *M. tuberculosis*. It has a remarkably low toxicity and low chemotherapeutic index. *Antimicrobial action of terramycin in vitro and in vivo, G. L. Hobby, N. Dougherty, T. F. Lenart, E. Hudders, & M. Kiseluk, Proc. Soc. Exper. Biol. & Med., March, 1950, 73: 503.—(F. B. Seibert)*

LABORATORY STUDIES

"Cord Factor" and Virulence.—Virulent tubercle bacilli growing in the depth of, or on, the surface of a liquid medium form tight bundles or "cords" consisting of bacilli in close parallel arrangement. The same is true of virulent bacilli growing on the surface of solid media. Only virulent organisms and some BCG strains form cords; the cells of most avirulent strains are not oriented and tend to form irregular clumps. If a chemical factor related to virulence causes the bacilli to adhere to one another and is located at the surface of the cell, it might be removed easily by extraction. Wet virulent bacilli in mineral oil did not lay in typical cords, but their morphology and tinctorial properties were unchanged. Petroleum ether broke up cords of wet bacilli within a few seconds as though some binding substance were removed. The bacteria-free petroleum ether extract was evaporated and repeatedly reprecipitated from ether with ethanol to obtain a precipitate of colorless, amorphous, waxy "cord factor." Avirulent variants of tubercle bacilli did not yield such material; only small amounts could be obtained from BCG. Cells of *B. subtilis* and of avirulent tubercle bacilli coated with this material inhibited the migration of leukocytes which engulfed them in the same way as did virulent bacilli. Uncoated avirulent bacilli and virulent bacilli after extraction had no effect on the migration of the phagocytes. "Cord factor" from virulent tubercle bacilli (H37Rv) repeatedly injected in small doses into mice was toxic; a single large dose was not. The susceptibility of the mice to this toxic action paralleled to some extent their susceptibility to infection with the strain of tubercle bacilli from which the fraction was obtained. Previously infected tuberculin-positive guinea pigs injected intradermally with the "cord factor" and with tuberculin reacted to the latter but not to the former, suggesting that the "cord factor" does not contain tuberculin. Injection of the "cord factor" into normal guinea pigs did not induce a state of allergic reactivity towards tuberculin. When unextracted virulent bacilli and bacilli extracted with petroleum ether were planted on Tween-agar plates, the only difference observed was a faster initial growth of the unextracted bacilli. The total growth was the same even when the extracted bacilli had been in prolonged contact with the petroleum ether. Extracted virulent bacilli were pathogenic for mice and guinea pigs but in some of the guinea pigs

the disease developed much more slowly than that due to unextracted bacilli. The extracted bacilli may have been phagocyted more readily than the unextracted ones. If the former were phagocytized before they formed new "cord factor," they may have been destroyed by the phagocytes. There is no evidence that the possession of "cord factor" is the only difference between virulent and avirulent strains of tubercle bacilli. The "cord factor" is acid-fast and the only identifiable acid-fast substance obtained from *Mycobacteria* is mycolic acid. The present preparation of "cord factor" may be either a crude mixture contaminated with mycolic acid or a new acid-fast lipid of the tubercle bacillus.—*Studies on the virulence of tubercle bacilli. Isolation and biological properties of a constituent of virulent organisms, H. Bloch, J. Exper. Med., February 1, 1950, 91: 197*—(*J. S. Woolley*)

Tuberculin Skin Test and Leukocyte Cytolysis.—Guinea pigs sensitized by the injection of heat-killed tubercle bacilli (H37Rv) in paraffin oil showed an increase in the *in vitro* tuberculin leukocyte cytolysis within 48 hours after a postive intracutaneous tuberculin reaction. Similar cytolysis occurred when PPD or OT was used as the skin-testing antigen. —*Increased in vitro tuberculin leucocyte cytolysis following a tuberculin skin test, C. B. Favour, B. A. Harrison, & C. K. Osgood, Proc. Soc. Exper. Biol. & Med., January, 1950, 73: 122.*—(*F. B. Seibert*)

Pyribenzamine in Tuberculin Shock.—Guinea pigs were sensitized to tuberculin by injection with BCG. Several experiments then were performed in which 2 to 12 mg. per kg. of pyribenzamine were given intracutaneously before or after intraperitoneal shocking doses of 3.3 to 10 ml. of OT 1:5. No evidence of protection from tuberculin shock was observed. The majority of highly sensitive guinea pigs were protected from severe shock and death caused by other antigens. The results support the concept that anaphylactic and tuberculin sensitivities are basically different.—*Tuberculin reaction: IV. Failure of pyribenzamine to protect against systemic tuberculin shock, R. S. Weiser, E. Evans, & L. St. Vincent, Proc. Soc. Exper. Biol. & Med., February, 1950, 73: 303.*—(*F. B. Seibert*)

Bacterial Filtration by Gauze.—Lurie and Abramson found that 90 to 95 per cent of droplet nuclei of virulent tubercle bacilli in the air respired by rabbits is removed by 3- to 6-layered gauze masks properly worn by the animals breathing infected air. The author measured the threads and the interthread spaces of the masks worn by the above rabbits. He found that the sizes of both entities had normal distribution curves and that the statistical space-thread ratio was 1.67 to 1.00. Three layers of gauze would thus result in complete coverage of a large portion of the total area. If it is assumed that the tubercle bacilli on coming in contact with the threads adhered to them under the conditions of the above experiments, the geometry of the superimposed gauze layers would provide a barrier against the free passage of the bacilli in the air stream. This "occlusion by impact" would be effective against well over 90 per cent of the bacteria inhaled through the masks.—*An analysis of the mechanism of the bacterial filtering action of gauze masks, H. Shapiro, Am. J. Hyg., March, 1950, 51: 135.*—(*Max B. Lurie*)

Bronchial Anastomosis.—The bronchi were divided and anastomosed in 33 dogs. Results were far better after closure with cuffs everted by horizontal mattress sutures than after simple end-to-end closures. Possible clinical applications are in traumatic rupture of the bronchus, adenoma or benign tumor requiring resection, local strictures from any cause with normal parenchyma distally, and accidental severing of the bronchus during surgery. The majority of the silk sutures used are cast off into the lumen of the bronchus. The use of rigid clamps on the proximal stump before closure would seem hazardous in pulmonary resection because in 2 dogs in which they were used bronchopleural fistulas occurred.—

An experimental study in bronchial anastomosis, T. L. Jackson, P. Lefkin, W. Tuttle, & F. Hampton, J. Thoracic Surg., October, 1949, 18: 630.—(R. E. MacQuigg)

Adrenaline and Respiration.—Respiration in the vagotomized medullary animal after carotid artery ligation or section of the glossopharyngeal nerves is arrested by intravenous injections of adrenaline. It is concluded that apnea in these circumstances is due to direct inhibition of the respiratory center by adrenaline, akin to adrenaline inhibition of sympathetic ganglionic transmission and auditory and optical cortical potentials. (Authors' summary).—*Adrenaline apnea in the medullary animal, H. E. Hoff, C. G. Breckenridge, & J. E. Cunningham, Am. J. Physiol., March 1, 1950, 160: 485.—(G. C. Leiner)*

Anoxia in Explosive Decompression.—In experiments in which rats were explosively decompressed to 21 mm. of mercury (an altitude equivalent of 80,000 feet), subsequent time at this reduced pressure was found to be directly correlated with survival. Pre-oxygenation (2 atmospheres for 30 minutes) did not materially affect survival following decompression. Alterations in metabolic rate, and inferentially in oxygen consumption, through exposure to cold or injection of thyroxin gave evidence that post-decompression survival was correlated with oxygen demand. Both carbon dioxide pre-breathing to produce respiratory excitation and cerebral hyperemia and adrenaline injection to effect cardiovascular stimulation were found to increase post-decompression tolerance of rats to the rarefied environment. These findings were interpreted as indicative of the major importance of anoxic anoxia as a causative factor in death resulting from explosive decompression injury (Authors' summary).—*Anoxia in explosive decompression injury, W. M. Hall & E. L. Corey, Am. J. Physiol., February 1, 1950, 160: 361.—(G. C. Leiner)*

Cardio-Respiratory Events in Anoxia.—An empirical formula has been developed to predict pulmonary ventilation in dogs with 3 types of anoxia, using oxygen saturation, carbon dioxide tension, pH, and diastolic and venous blood pressures. The error involved (one root mean square deviation) in attempting a prediction of pulmonary ventilation from these measurements has been found to be about 2 in 13 ventilation units, one ventilation unit being defined as the dog's pulmonary ventilation at rest. It has been shown that the breathing in anoxia does not bear a linear relation to the oxygen-saturation but rather that the breathing is best related to the oxygen-saturation by means of a cubic equation. A multiple factor analysis of the dogs' physiological behavior in anoxia has also been made, resulting in further emphasis upon the mutual interdependence of all the measurements taken. The pH and the pCO_2 appear to be 2 of many prime factors in the dogs' over-all reactions to anoxia (Authors' summary).—*Interrelationship of the cardio-respiratory events in anoxia, M. Brucer, G. L. Herman, & H. G. Swann, Am. J. Physiol., January 1, 1950, 160: 138.—(G. C. Leiner)*

A New Catheter for Bronchospirometry.—The single lumen catheter introduced by Norris and associates in 1948 is a great advance in bronchospirometry. The largest size of this catheter offers approximately one-fifth the resistance to air flow offered by one channel of the largest size of Zavod's double-lumen catheter. Sometimes, however, there is difficulty in determining fluoroscopically if the inflatable cuff is placed just between the carina and the mouth of the left upper lobe bronchus. To avoid this difficulty and to obviate fluoroscopy a flexible double lumen rubber catheter has been constructed of approximately the same rigidity as an ordinary urethral catheter. It is provided with a little hook which is automatically engaged by the carina. The lumen of each channel in the largest model is the same size as the single lumen catheter of Norris and associates. For women a somewhat smaller size is used. In introduction the rubber hook is tied down to the catheter with a silk thread to facilitate the intro-

duction through the larynx, the knot being so tied that it is easily opened by pulling one end of the thread. The catheter is then introduced over a stylet under mirror guidance, turned 90 degrees to the left, and advanced until the hook is engaged by the carina. It is very easy to feel when the catheter is in the correct position. The cuffs are inflated with a syringe until the control bags on the upper part of the capillary air leads are distended and are then clamped off. By observing the tension in the control bags it is easy to obtain the required distension of the cuffs, eliminating the necessity for manometric control of the pressure in the cuffs. Premedication and topical anesthesia are approximately those employed for bronchoscopy. It is of great importance to give only a small dose of morphine in order not to depress the activity of the respiratory center. Over 60 bronchospirometric examinations have been made with no difficulty in introduction or untoward effect. After premedication with atropine or methylscopolamine there has been no obstruction by secretions even when the examination was continued for an hour. The summation of the vital capacities from both lungs gives a very close correlation with the results obtained by ordinary spirometry without any introduced stenosis. The lumina of the channels are large enough to permit bronchospirometric examination on patients exercising on a cycle ergometer in studying oxygen absorption in an affected lung.—*A new flexible double lumen catheter for bronchospirometry, E. Carlens, J. Thoracic Surg., October, 1949, 18: 742.—(R. E. MacQuigg)*

Pulmonary Arterial Pressure.—The pulmonary arterial pressure was measured in a reptile and in a bird. The average was 35/12 mm. of mercury in the turtle, and 24/12 mm. of mercury in the chicken. The average pulmonary arterial pressure in the dog is 28/10 mm. of mercury. While systemic arterial pressures are different in the various classes of vertebrates, pulmonary arterial pressures are almost the same. "The pulmonary arterial pressure remains low in the higher vertebrates, probably as a result of factors which act to increase the rate of exchange of blood gases with those of the environment. These include: (a) the enormous pulmonary vascular bed, (b) the absence of tissue support of the pulmonary capillaries which are exposed over nearly their entire surface to the environment, resulting in (c) the great distensibility of the capillaries permitting little increment in pressure with greatly increased volume. An increased pressure in such a capillary would produce a transudate and result in disturbed respiratory function."—*The pulmonary arterial pressure, S. Rodbard, F. Brown, and L. N. Katz, Am. Heart J., December, 1949, 38: 863.—(G. C. Leiner)*

Vapor Retention in Nose and Lung.—In formulating the problem of the gas exchange of the respiratory barrier it generally is assumed that the gas exchanged is in equilibrium with the gas in solution except for the "dead air space." The factors involved in this aspect of gas exchange were evaluated in man. For the most nearly normal breathing pattern (inspiration of 18 liters per minute) about 65 per cent of inhaled alcohol vapor was retained in the lung. The corresponding percentages for hydrogen cyanide, acetone vapor, and ammonia were 58, 55, and 92, respectively. The percentage retained was not appreciably affected by the concentration of the material in the air. A threefold increase of the depth of breathing, the temporal pattern being kept constant, had no appreciable effect on the percentage retained. A threefold increase of the mean time during which the material remained in the lung resulted in only a moderate increase in the percentage retained. The amount of alcohol vapor retained in the human nose was found to be about 48 per cent for a flow rate of 18 liters per minute. For hydrogen cyanide, acetone vapor, and ammonia, the percentages retained in the nose were about 22, 18, and 83.—*Retention of vapors and gases in the human nose and lung, H. D. Landahl & R. G. Herrmann, Arch. Indust. Hyg. & Occup. Med., January, 1950, 1: 36.—(T. H. Noehren)*

Fate of Inhaled Oil Aerosol.—Mice were exposed to mists of particulate liquid oils having average mass median diameters of 2.5 microns. Droplets of oil retained in the lungs were found to be dispersed evenly from apex to base and hilus to pleura, and were immediately phagocytosed. Phagocytosis was essentially completed within forty-eight hours except after prolonged exposures of two to four weeks when large numbers of free droplets were seen in the lungs. The initial concentrations of retained oil droplets were similar for all the oil mists used. After exposure to edible oil droplets (corn, peanut, and cod-liver oils), the concentration of retained oil decreased progressively during the succeeding ninety-six hours; after exposure to liquid petrolatum and motor oil, the concentrations remained essentially unchanged. After heavy exposures for periods of two to four weeks, liquid petrolatum and motor oil droplet retention resulted in localized foreign-body reactions of moderate severity as well as some patches of lipid pneumonia. Cod-liver oil droplets caused a moderate foreign-body reaction. There were negligible reactions to peanut oil and corn oil droplets.—*Distribution, effect and fate of oil aerosol particles retained in the lungs of mice, M. Shoshkes, W. G. Banfield, & S. J. Rosenbaum, Arch. Indust. Hyg. & Occup. Med., January, 1950, 1: 20.*—(*T. H. Noehren*)

Inhalation of Oil Fogs.—Mice, rats, rabbits, and monkeys were exposed to fogs composed of oil particles for periods of 100 to 365 consecutive days in order that the possible dangers for men working in such atmospheres might be investigated. Ordinary automobile oil and S.G.F. no. 1 oil were tested, the latter being used by the United States Army Chemical Corps for smoke-screening of troops. Mice, rats, and rabbits were unaffected and the occurrence of pulmonary tumors in a highly susceptible strain of mice was not accelerated by the oil fog. Surprisingly little oil accumulated in the lungs of the animals, and what was retained was rapidly transferred into the pulmonary connective tissues and lymph nodes. Lipid pneumonia was found not to be a hazard of living in atmospheres containing 63 to 132 micrograms of oil per liter of air because the low pulmonary retention enabled the phagocytes of the lung to engulf and remove it adequately. The incidence of infectious pneumonia in monkeys exposed to such fogs was greatly increased, although most monkeys so treated died with severe hyperplastic gastritis as previously reported (Authors' summary).—*Effects of prolonged inhalation of oil fogs on experimental animals, C. C. Lushbaugh, J. W. Green, Jr., & C. E. Redemann, Arch. Indust. Hyg. & Occup. Med., February, 1950, 1: 237.*—(*T. H. Noehren*)

PUBLIC HEALTH AND EPIDEMIOLGY

Examination of Tuberculosis Contacts.—A review of the available data led to a recommendation that quarterly examinations be made of contacts with known cases of tuberculosis for one year after exposure. This control may be exercised semiannually during the next two years and annually thereafter. Among 1,847 contacts examined at the Belo Horizonte dispensary the rate of tuberculosis infection found during the first year of the follow-up period was 13.9 per cent, varying from 27 per cent in children less than three years old to 5.3 per cent in persons over 46 years old. Among 768 children aged four to fourteen years the rate was 12.5 per cent, much higher than that found in New York surveys. Three-fourths of the cases were discovered during the first examination. Even after the heavy early screening, 3.26 per cent of 1,318 contacts judged to be normal when first seen proved tuberculous at the second examination.—*Com que freqüência devem ser examinados os contactos de tuberculose?, J. Feldman & A. de Oliveira Lucena, Rev. brasil. tuberc., September–October, 1949, 17: 451.*—(*A. A. Moll*)

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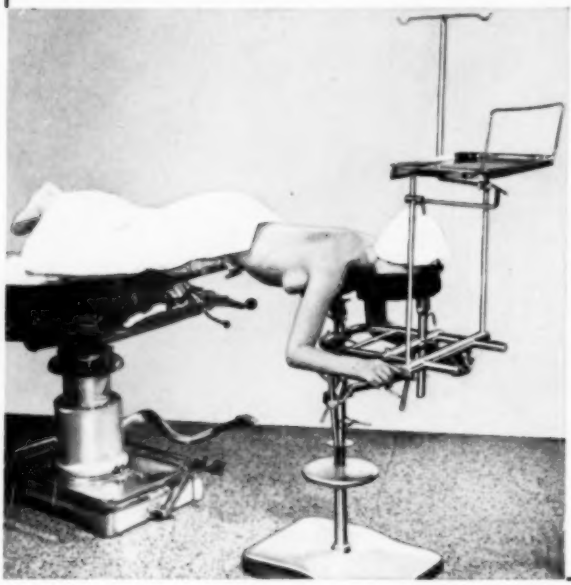

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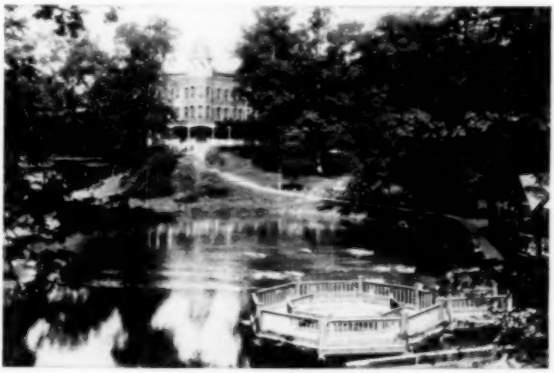

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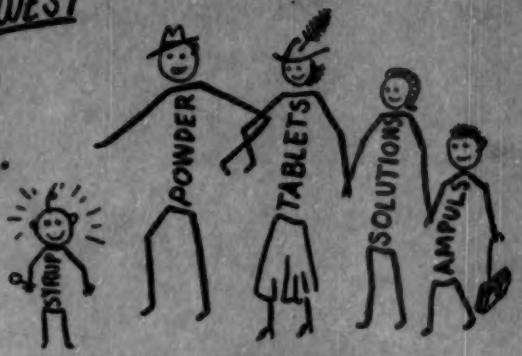

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